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**Collected By Dr.Ahmed Manfy**

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# Probiotics and Human Milk Oligosaccharides in Premature Infants

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## Education Gap

Understanding of the role of the intestinal microbiota in the premature infant is evolving; this community of microbes is important in the development of necrotizing enterocolitis and sepsis.

## Abstract

Intestinal dysbiosis precedes and is a likely causative factor in necrotizing enterocolitis (NEC) and many cases of late-onset sepsis. Randomized controlled trials and observational cohort studies demonstrate decreased risk of NEC, sepsis, and death with the administration of probiotic microbes and decreased risk of NEC and sepsis with feeding of human milk. Animal studies suggest promising mechanisms by which probiotic microbes and human milk oligosaccharides alter the composition of the intestinal microbiota and may prevent disease in premature infants. Inclusion of parents in discussions of the risks and benefits of human milk and probiotics for premature infants is essential.

## Objectives After completing this article, readers should be able to:

1. Summarize the translational and clinical evidence that human milk and probiotics decrease the risks of necrotizing enterocolitis, death, and sepsis in premature infants.
2. Summarize known functions of human milk oligosaccharides.

**AUTHOR DISCLOSURE** Dr Underwood has disclosed that he has received honoraria for lectures on human milk oligosaccharides from Abbott Nutrition and led a clinical trial of probiotic *Bifidobacterium infantis* that was funded by Evolve Biosystems. The funding source for this article is NIH R01 HD059127 and UL1 TR000002. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

CMV	cytomegalovirus
GOS	galacto-oligosaccharide
HIV	human immunodeficiency virus
HMOs	human milk oligosaccharides
NEC	necrotizing enterocolitis
RCT	randomized controlled trial
RR	risk ratio

## INTRODUCTION

Dysbiosis refers to an alteration of the microbial composition of a given anatomic niche that is associated with disease. Well-recognized acute diseases triggered by intestinal dysbiosis in children and adults include antibiotic-associated diarrhea and *Clostridium difficile* colitis. Increasing evidence suggests that intestinal dysbiosis also plays an important role in the pathogenesis of many chronic diseases of children and adults including allergic and autoimmune diseases. (1)(2) In the premature infant, intestinal dysbiosis appears to be an important trigger for



necrotizing enterocolitis (NEC) and sepsis. Threads of evidence that support this association include:

- 1) The timing of onset—NEC incidence peaks at 27 to 32 weeks' postmenstrual gestational age, (3) which correlates with the peak predominance of fecal proinflammatory proteobacteria (4)
- 2) Increased risk of NEC in infants receiving antibiotics or acid-suppressing agents both of which alter the intestinal microbiota (5)(6)(7)(8)
- 3) Associations between chorioamnionitis/funisitis and increased risk of sepsis weeks later (9)
- 4) Confirmation of the presence of bacterial species in the feces of preterm infants, which are identical to those isolated from the bloodstream in sepsis (10)
- 5) Decreased risk of NEC and sepsis with feeding of human milk and/or administration of probiotics, both of which alter the intestinal microbiota (11)(12)(13)(14)
- 6) Carefully conducted studies of changes in the fecal microbiota that occur before the onset of NEC, most commonly an increase in proteobacteria and decreases in firmicutes and bacteroides. (15)

This article includes a brief review of 1) the evidence that probiotics and human milk prevent NEC, death, and sepsis; 2) the risks associated with probiotics and human milk; and 3) the evidence that human milk oligosaccharides (HMOs) play a role in this protection.

## PROBIOTICS

### Benefits

Probiotics are dietary supplements that contain live bacteria. Animal and in vitro studies have been useful in elucidating mechanisms by which probiotics exert their beneficial effects, including production of bacteriocins (16)(17); suppression of expression of proinflammatory cytokines (18)(19) (20)(21)(22); stimulation of expression of anti-inflammatory cytokines (23)(24); stimulation of intestinal motility (25) (26); regulation of apoptosis, autophagy, and intestinal permeability (27)(28)(29)(30); production of short chain fatty acids (31); and binding to host mucosa and/or mucus. (32)(33) A recent meta-analysis summarized the probiotic strains most useful in preventing NEC in animal models. (34)

The large number of randomized placebo-controlled probiotic trials in premature infants reporting NEC, death, and sepsis has been the subject of several meta-analyses, results of which are summarized in Table 1. (35)(36)(37)(38) (39)(40)(41)(42)(43) Although several of the individual trials were small and the meta-analyses used varied statistical

approaches, the results of each meta-analysis have been similar: administration of probiotics to premature infants decreases the risk of NEC and death, with most but not all meta-analyses demonstrating decreased risk of late-onset sepsis and shorter time to full enteral feeding. The following statement from the most recent update of the Cochrane review is compelling: "Enteral supplementation of probiotics prevents severe NEC and all-cause mortality in preterm infants. Our updated review of available evidence strongly supports a change in practice. Head-to-head comparative studies are required to assess the most effective preparations, timing and length of therapy to be utilized." (44) A recent more extensive meta-analysis that also included non-English manuscripts (51 randomized controlled trials [RCTs] including 11,231 preterm infants) focused on comparisons of benefit by probiotic strain, results of which are summarized in Table 2. (45) A meta-analysis comparing single organism probiotic products to multiple organism products found the latter to be more likely to prevent NEC. (46) A meta-analysis of RCTs reporting outcomes for extremely low-birthweight infants did not find evidence for benefit in this subset that is at particularly high risk for NEC (1,618 extremely low-birthweight infants in 6 RCTs, risk ratio [RR] for NEC stage 2 or 3 of 0.86 [95% confidence interval [CI] 0.64–1.16]). (37) Finally, a meta-analysis of 14 RCTs of probiotic administration to premature infants that reported surgical NEC as an outcome found no difference in stage 3 NEC between groups (3,975 preterm infants, RR 0.74 [95% CI 0.51–1.05]), but did find a lower risk of NEC-related death in the probiotic group (13 studies, RR 0.56 [95% CI 0.34–0.93]). (47)

In addition to these RCTs, 24 observational studies of probiotic administration to premature infants have been published to date. The first 12 and 14 were included in 2 meta-analyses which showed decreases in NEC, death, and sepsis that were similar to those seen in the RCTs. (39)(48) Ten more recent observational studies have been published. Four are of particular interest, in that 2 found no statistically significant benefit in NEC reduction (though 1 did find benefit only in the human milk-fed subgroup) (49)(50); 2 demonstrated an *increase* in NEC during the period of probiotic administration (the only published studies to date to demonstrate a worse outcome in this population) (51)(52); and the other 6 showed benefits similar to those seen in previous studies, including a very large cohort study of 44 NICUs in Germany. (53)(54)(55)(56)(57)(58) The combined unweighted odds ratios for all 24 observational studies are summarized in Table 3.

TABLE 1. **Meta-analyses of Probiotic Studies in Premature Infants**

REFERENCE	YEAR	TRIALS	INFANTS	RR (95% CI)
NEC (stage 2 or 3)				
AlFaleh and Anabrees (35)	2014	20	5529	0.43 (0.33-0.56)
Yang et al (36)	2014	17 <sup>a</sup>	4198	0.34 (0.25-0.45)
Sawh et al (37)	2016	35	10,520	0.53 (0.42-0.66)
Deshpande et al (38)	2017	20 <sup>b</sup>	4022	0.46 (0.34-0.61)
Dermyshe et al (39)	2017	29	8535	0.57 (0.47-0.70)
Thomas et al (40)	2017	23	7325	0.57 (0.43-0.74)
All-cause mortality				
AlFaleh and Anabrees (35)	2014	17	5112	0.65 (0.52-0.81)
Yang et al (36)	2014	14 <sup>a</sup>	3583	0.58 (0.46-0.75)
Sawh et al (37)	2016	27	9507	0.79 (0.68-0.93)
Deshpande et al (38)	2017	19 <sup>b</sup>	4196	0.73 (0.59-0.90)
Dermyshe et al (39)	2017	27	8156	0.77 (0.65-0.92)
Thomas et al (40)	2017	23	6954	0.72 (0.57-0.92)
Late-onset sepsis				
Yang et al (36)	2014	17 <sup>a</sup>	4043	0.94 (0.83-1.1)
Sawh et al (37)	2016	28	8707	0.88 (0.77-1.0)
Rao et al (41)	2016	37	9416	0.86 (0.78-0.94)
Deshpande et al (38)	2017	18 <sup>b</sup>	4062	0.80 (0.71-0.91)
Dermyshe et al (39)	2017	28	7987	0.88 (0.80-0.97)
Aceti et al (43)	2017	20 <sup>c</sup>	3402	0.75 (0.65-0.85)
Time to full enteral feedings				Mean difference (95% CI)
Yang et al (36)	2014	9 <sup>a</sup>	1626	-1.66 days (-3.6 to 0.27)
Aceti et al (43)	2016	5 <sup>d</sup>	719	-3.15 days (-5.3 to -1.1)
Sawh et al (37)	2016	17	4448	-1.2 days (-2.2 to -0.1)
Deshpande et al (38)	2017	13 <sup>b</sup>	2154	-1.95 days (-3.4 to -0.45)

CI=confidence interval; NEC=necrotizing enterocolitis; RR=relative risk.

<sup>a</sup>English and Chinese language publications.

<sup>b</sup>Low and middle income countries only.

<sup>c</sup>Included only studies with exclusively human milk-fed premature infants; 16 studies of exclusive formula feeding showed no significant decrease in late-onset sepsis with probiotic administration (800 premature infants; RR 0.77 (95% CI 0.51-1.17)).

<sup>d</sup>Included only studies with exclusively human milk-fed premature infants; 2 studies of exclusive formula feeding showed no benefit in time to full enteral feeding with probiotic administration.

## Risks

In the United States, less than 15% of neonatal intensive care units currently administer probiotics to premature infants. (59) The US Food and Drug Administration does not monitor the purity and viability of probiotic products and does not recommend administration of probiotics without oversight through the Investigational New Drug program.

The American Academy of Pediatrics does not recommend probiotic administration because of the lack of products with established safety and efficacy. Safety concerns include contamination of commercial probiotic products with potential pathogens (60) and sepsis caused by translocation of a probiotic organism into the bloodstream. (61) The evidence from the RCTs that death and sepsis are

TABLE 2. Strain-Specific Summary of Beneficial Probiotics

PROBIOTIC STRAIN	NO. OF STUDIES	NO. OF INFANTS	RR (95% CI)
NEC (stage 2 or 3)			
<i>Bifidobacterium lactis</i> Bb12 or B94	5	828	0.25 (0.10-0.56)
<i>Lactobacillus reuteri</i> 55730 or 17938	4	1459	0.43 (0.16-0.98)
<i>Lactobacillus rhamnosus</i> GG	6	1507	0.24 (0.06-0.67)
<i>Bifidobacterium bifidum</i> , <i>Bifidobacterium infantis</i> , <i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i>	2	247	0.25 (0.05-0.89)
<i>B. infantis</i> 15697, <i>L. acidophilus</i> 4356	1	367	0.16 (0.02-1.0)
<i>B. infantis</i> Bb02, <i>B. lactis</i> Bb12, <i>Streptococcus thermophilus</i> TH4	2	1244	0.29 (0.07-0.78)
<i>B. longum</i> 35624, <i>L. rhamnosus</i> GG	2	285	0.18 (0.02-0.89)
All-cause mortality			
<i>B. bifidum</i> 1453 + <i>L. acidophilus</i> 1748	2	494	0.16 (0.02-0.74)
<i>B. bifidum</i> , <i>B. infantis</i> , <i>B. longum</i> , <i>L. acidophilus</i>	1	186	0.26 (0.06-0.98)
<i>B. infantis</i> , <i>L. acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus plantarum</i> , <i>L. rhamnosus</i> , <i>S. thermophilus</i>	1	150	0.09 (0.003-0.70)
Late-onset sepsis			
<i>B. bifidum</i> , <i>B. infantis</i> , <i>B. longum</i> , <i>L. acidophilus</i>	2	247	0.43 (0.18-0.94)
<i>B. longum</i> R00175, <i>Lactobacillus helveticus</i> R0052, <i>L. rhamnosus</i> R0011, <i>Saccaromyces boulardii</i> CNCM I-1079	3	241	0.34 (0.16-0.66)
Time to full enteral feedings (days)		Mean difference (95% CI)	
<i>L. reuteri</i> 55730 or 17938	3	626	-3.3 d (-6.4 to -0.62)
<i>B. bifidum</i> , <i>B. infantis</i> , <i>B. longum</i> , <i>L. acidophilus</i>	2	247	-4.7 d (-8.6 to -0.7)
<i>B. longum</i> BB536, <i>L. rhamnosus</i> GG	1	94	-10 d (-16 to -3.6)

Data from van den Akker et al. (45) CI=confidence interval; NEC=necrotizing enterocolitis; RR=relative risk.

consistently either lower or equivalent in the infants receiving the probiotic compared with those receiving the placebo suggests strongly that the risks of probiotic sepsis are very low. Secondary analyses of probiotic trials in preterm infants reporting other outcomes including intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, and neurodevelopmental outcomes have shown neither benefit nor negative effects, suggesting that probiotics are safe. (62)(63)(64)(65)(66)

## HUMAN MILK OLIGOSACCHARIDES

### Benefits

Administration of mother's own milk particularly in the first weeks after birth decreases the risk of NEC and sepsis. (11)

(67) A meta-analysis of the few RCTs in premature infants comparing formula to donor human milk demonstrated a higher risk of NEC with formula than with donor milk (RR 2.8 [95% CI 1.4-5.5]). (12) Multiple components of human milk are likely responsible for these protective effects, including antibodies (mostly secretory immunoglobulin [Ig] A but also IgG and IgM), lactoferrin, lysozyme, growth factors, enzymes and HMOs. HMOs are nondigestible glycans that are produced in abundance in human milk with a high number of structures and striking diversity of structures among women. The obvious question is why does a mother produce such a large volume of diverse HMOs at great cost if these glycans have no nutritional value to her infant? Three compelling hypotheses are supported by current evidence. First, HMOs are an energy source for a



TABLE 3. **Observational Cohort Studies of Probiotic Administration in Premature Infants**

	NO PROBIOTIC (CASES/N)	PROBIOTIC (CASES/N)	ODDS RATIO (95% CI)
Necrotizing enterocolitis stage 2 or 3	831/16,587 (5.0%)	432/15,111 (2.9%)	0.56 (0.50-0.63)
All-cause mortality	1144/14,165 (8.1%)	981/14,383 (6.8%)	0.83 (0.76-0.91)
Late-onset sepsis	2,083/12,932 (16%)	1,950/13,141 (15%)	0.91 (0.85-0.97)

very limited number of species of bacteria. Unlike commercial prebiotic glycans, such as galacto-oligosaccharides (GOSs), fructo-oligosaccharides, inulin, and lactulose, which can be consumed by a wide variety of gut microbes, intact HMOs can be consumed by only 2 bacterial genera: *Bacteroides* and *Bifidobacterium*, and in fact among the bifidobacteria, only a few species (eg, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *B longum* subspecies *longum* and *B longum* subspecies *infantis*) are aggressive consumers of HMOs. (68) Although HMOs play a major role in shaping the microbiota of the term infant, the effect of maternal HMO composition in the preterm infant is more subtle. (69)(70) This is not surprising because 1) neither *Bacteroides* nor *Bifidobacterium* species are common in the premature infant microbiota unless the infant is receiving probiotic organisms, and 2) environmental factors play a major role in shaping the gut microbiota in this hospitalized population. We also found higher variability in HMO composition in the milk of women delivering preterm infants compared with those delivering at term. (71) Thus, the lactating woman invests energy to produce HMOs to shape the intestinal microbiota of her infant, but this appears to have less impact in premature infants than in term infants. Second, HMOs have similar structures as the surface glycans on enterocytes to which intestinal bacteria and viruses are able to adhere. In vitro studies have demonstrated decreased binding of *Campylobacter jejuni* and *Pseudomonas aeruginosa* in the presence of 2 common HMOs (2'fucosyllactose and 3 fucosyllactose) (72) and effective binding of these same HMOs to the site on the norovirus particle that adheres to host enterocytes. (73) Human studies have demonstrated decreased risk of infectious diarrhea in infants whose mothers had higher levels of specific HMOs in their milk. (74) Thus, lactating women produce HMOs to protect their infants from diarrheal illness. Third, HMOs appear to affect the developing immune system. Infants randomly assigned to receive formula containing GOS plus a single common HMO structure (2'fucosyllactose) had lower serum levels of

proinflammatory cytokines and a lower incidence of atopic dermatitis than the infants who received a formula with GOS but no added HMO. (75)(76) In a separate study, infants receiving formula with 2 added HMOs (2'fucosyllactose and lacto-n-neotetraose) had fewer parent-reported episodes of lower respiratory infections, fevers, and antibiotic courses than infants receiving a formula without HMOs. (77) Thus, lactating women produce HMOs to influence their infants' immune responses.

### Risks

Human milk is recommended as the primary enteral nutrition for premature infants, particularly those with birthweights less than 1,500 g, with donor human milk recommended when available if the volume of mother's milk is insufficient. (78) The major risks of providing unpasteurized mother's own milk are transmission of viral infections. The risk of human immunodeficiency virus (HIV) infection is sufficient to support current recommendations for HIV-infected mothers in developed countries to avoid breastfeeding. (79) The risk of infection with either hepatitis B or hepatitis C through mother's milk is very low, (80) but the risk of cytomegalovirus (CMV) infection in very premature infants is not insignificant. Most recent estimates are quite sobering; prospective cohort studies show infection rates among very preterm infants with CMV-positive mothers of 15% to 100%, with the most premature infants and infants of mothers with the highest DNA load at highest risk. (81)(82)(83)(84) Symptomatic CMV infection and severe sepsislike syndrome are uncommon, with the latter ranging from 0% to 14% of CMV infections (82); however, associations between CMV infection and increased risk of bronchopulmonary dysplasia and retinopathy of prematurity have been reported. (83)(84) Freezing of human milk does not decrease the risk for CMV infection. (85) Pasteurization of donor human milk is highly effective at killing HIV, hepatitis C, and CMV.

The primary risk with donor human milk is poor growth and development. Donor milk is generally provided by mothers who delivered at term and have been breastfeeding for a time. As a result, the milk is often low in protein and must generally be fortified to provide adequate growth. Although current pasteurization techniques denature many of the bioactive proteins and peptides in human milk, HMOs are quite heat resistant and therefore pooled donor human milk is a good source of HMOs.

## SYNERGISM BETWEEN HUMAN MILK AND PROBIOTICS

Among the probiotic clinical trials published to date, few have reported how many of the infants in each group received human milk. Among those reporting this important covariate, the infants receiving the combination of human milk and probiotics had a lower risk of NEC than infants receiving probiotics and formula. Researchers at University of California (UC) Davis have hypothesized over the last 15 years that combining administration of human milk (rich in HMOs) with a probiotic that is able to consume HMOs would improve colonization of the gut with the administered probiotic. This was found to be true in premature infants in comparisons of 2 common probiotic bifidobacteria: *Bifidobacterium longum* subsp *infantis* (the most aggressive HMO consumer among the many analyzed) and *Bifidobacterium animalis* subsp *lactis* (a non-consumer of HMOs). In both formula-fed and human milk-fed premature infants, *B infantis* was a better colonizer than *B lactis* and the greatest increases in fecal bifidobacteria and decreases in fecal proteobacteria were seen with the combination of human milk and *B infantis*. (14) Animal studies have confirmed that combining HMO-consuming probiotics and either synthetic HMOs or bovine milk oligosaccharides improves colonization with the administered organism. (31)(86) In a recent trial among breastfed term infants, administration of *B infantis* for a brief period (from 7-28 days of age) quickly led to domination of the infant fecal microbiota with the administered probiotic to such an extent that the usual differences in the microbiota between infants born via cesarean section and infants delivered vaginally were attenuated. The hypothesis was that once the infants were colonized with this HMO-consuming probiotic, colonization would be maintained as long as the infants were receiving human milk. Indeed, at 2 months of age, *B infantis* remained the dominant organism in the feces, a full month after stopping the probiotic. (87) Whether such an approach will mitigate the risks of chronic diseases associated with

cesarean section delivery or intestinal dysbiosis in general remains uncertain.

## BRINGING PARENTS INTO THE DISCUSSION

At the first US symposium dedicated exclusively to NEC, held in Davis, CA, in April 2017, the involvement and inclusion of parents whose families have been affected by NEC was powerful. The symposium was cosponsored by the NEC Society (a nonprofit foundation started by 2 mothers whose infants died of NEC) and the Department of Pediatrics at UC Davis. The parents who attended the symposium were united in their profound expressions of appreciation for the research in NEC to date and their frustration and anguish at the relatively little information they received about NEC either before or even after disease onset. The united voice of the parents was that they need more information about NEC prevention early in their infant's life, including discussions about the risks and benefits of mother's own milk, pasteurized donor human milk, probiotics, and avoidance of unnecessary antibiotics and other medications that may increase the risk of NEC. (88) If, after review of the literature and a thoughtful discussion with the parents, a neonatologist decides that the potential benefits of providing a combination of human milk and probiotics outweigh the potential risks, a probiotic product that is manufactured to high standards and has been demonstrated to be effective should be chosen. The NEC Society (NECSociety.org) describes a probiotic quality improvement approach with descriptions of probiotics that meet those criteria and a plea to share quality improvement data. Further comparisons of probiotics to placebo are unlikely to provide new insights; rather, head-to-head comparisons of promising probiotics are needed and will require very large sample sizes.

## EVIDENCE

- The benefits of human milk outweigh the risks in premature infants, with the exception of HIV-infected mothers in developed countries and other maternal and infant conditions. The benefits of donor human milk outweigh the benefits of formula for very low-birthweight infants (meta-analysis, strong recommendation).
- The benefits of probiotic administration outweigh the risks in premature infants and justify a careful discussion with parents and a potential practice change (meta-analysis, strong recommendation).

# American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathophysiology of NEC.
- Know the differences between the composition of breast milk of the mother of a preterm infant and that of a full-term infant.
- Know the immunologic and anti-infective constituents in human milk and their physiologic effects.

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1. Alterations in the microbial composition of the gastrointestinal tract (dysbiosis) have been implicated in the pathophysiology of necrotizing enterocolitis (NEC). Which of the following statements does NOT support the role of dysbiosis in the pathophysiology of NEC?
  - A. The timing of NEC correlates with the peak predominance of firmicutes.
  - B. Infants receiving antibiotics have an increased risk for NEC.
  - C. Breastfed infants have a decreased risk for NEC.
  - D. Changes in fecal microbiota have been identified before the onset of NEC.
  - E. Bacterial species have been identified in stools which are identical to those isolated from blood cultures in preterm infants with sepsis.
2. Probiotics are dietary supplements containing live bacteria that have been shown to be protective against NEC in preterm infants. Which of the following represents a mechanism by which probiotics exert their protective effects?
  - A. Production of long-chain fatty acids.
  - B. Inhibition of bacterial motility.
  - C. Production of bacteriocins.
  - D. Inhibition of autophagy.
  - E. Binding to proinflammatory cytokines.
3. Several studies have evaluated the use of probiotics in preterm infants and have been included in meta-analyses. These studies support a decrease in NEC rates in preterm infants receiving probiotics. However, there remain questions regarding which preparation is most effective and when and how long to treat. Based on results from these meta-analyses, which statement is CORRECT regarding the use of probiotics in preterm infants?
  - A. Probiotic use is most effective in preventing NEC in extremely low-birthweight infants.
  - B. Probiotic administration decreases the rate of surgical NEC.
  - C. The most recent Cochrane review indicates that while probiotics prevent severe NEC, they do not decrease all-cause mortality in preterm infants.
  - D. Products containing multiple strains are more likely to prevent NEC compared with those containing a single organism.
  - E. A consistent decrease in the risk of late-onset sepsis is observed with probiotic administration.
4. Human milk feedings have been shown to decrease the risk of NEC and sepsis. Which of the following components of human milk is NOT thought to be responsible for the protective effects of human milk?
  - A. Lactoferrin.
  - B. Lysozyme.
  - C. Immunoglobulin A.
  - D. Human milk oligosaccharides (HMOs).
  - E. Lactose.

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5. HMOs are nondigestible glycans that are abundant in human milk. A wide diversity in the structure of HMOs as well as large diversity among women has led to several hypotheses regarding the function of HMOs. Which of the following statements regarding the role of HMOs is CORRECT?
- A. Similar to commercial prebiotic glycans, HMOs can be consumed by a wide variety of gut microbes.
  - B. Infants receiving formula with added HMOs have a lower incidence of atopic dermatitis.
  - C. HMOs have been shown to play a major role in shaping the microbiota of preterm infants, and to a lesser degree, term infants.
  - D. There is less variability in the HMO composition of preterm human milk compared with that of term human milk.
  - E. In vitro studies indicate that HMOs decrease binding of *Campylobacter jejuni* and *Pseudomonas aeruginosa* but not norovirus.

## Probiotics and Human Milk Oligosaccharides in Premature Infants

Mark A. Underwood

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**Probiotics and Human Milk Oligosaccharides in Premature Infants**

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# Gastrointestinal, Pancreatic, and Hepatic Manifestations of Cystic Fibrosis in the Newborn

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## Education Gap

Advances in newborn screening have led to earlier diagnoses of many patients with cystic fibrosis. Despite these advancements, some patients are not detected by newborn screen, and early recognition of clinical manifestations of cystic fibrosis remains critical. For most patients with cystic fibrosis, gastrointestinal signs and symptoms represent the earliest indication of disease. Furthermore, even for those in whom early detection is achieved, early manifestations of disease, such as reflux, dysbiosis, meconium ileus, poor weight gain, and cholestasis, present unique clinical and therapeutic challenges. Finally, it is imperative that providers recognize that early therapeutic interventions may impart a lifelong impact among patients with cystic fibrosis.

## Abstract

Gastrointestinal, pancreatic, and hepatic signs and symptoms represent the most common presentation of early disease among patients with cystic fibrosis and may be the initial indication of disease. Regardless of whether cystic fibrosis is diagnosed early by newborn screening or later by clinical course, the impact of gastrointestinal, pancreatic, and hepatic manifestations on early life is nearly ubiquitous. Conditions strongly linked with cystic fibrosis, such as meconium ileus and pancreatic insufficiency, must be recognized and treated early to optimize both short- and long-term care. Similarly, less specific conditions such as reflux, poor weight gain, and cholestasis are frequently encountered in infants with cystic fibrosis. In this population, these conditions may present unique challenges in which early interventions may have significant influence on both short- and long-term morbidity and mortality outcomes.

## Objectives

After completing this article, readers should be able to:

1. Recognize and treat common, early gastrointestinal, pancreatic, and hepatic manifestations of cystic fibrosis.
2. Understand that early interventions can have a long-lasting effect on the morbidity and mortality of patients with cystic fibrosis.

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### ABBREVIATIONS

AAP	American Academy of Pediatrics
AST	aspartate aminotransferase
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
EGD	esophagogastroduodenoscopy
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GGT	$\gamma$ -glutamyl transferase
H2RA	histamine-2 receptor antagonist
MII-pH	multichannel intraluminal impedance and pH measurement
PERT	pancreatic enzyme replacement therapy
PPI	proton pump inhibitor
SIBO	small intestinal bacterial overgrowth
ULN	upper level of normal

## INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive, multisystem disease affecting 1 in 2,000 to 1 in 4,000 newborns in the United States, with incidence varying by race and ethnicity. (1) It is caused by genetic mutations resulting in abnormal synthesis, structure, and/or function of the cystic fibrosis transmembrane regulator (CFTR) protein. The CFTR is a cyclic adenosine monophosphate-induced anion channel that transports chloride and bicarbonate across the apical surface of epithelial cells and may also regulate other important cellular functions. (2) Deficient CFTR function leads to altered mucus secretions in the luminal environment that can then lead to inflammation, obstruction, and dysfunction of various organs. (3)(4)

Respiratory disease remains the most frequent cause of morbidity and mortality in patients with CF, but gastrointestinal, pancreatic, and hepatobiliary disease are more commonly encountered in the first year of life. The widespread use of newborn screening has resulted in earlier diagnosis and improved outcomes for patients with CF, with many patients now diagnosed before the onset of clinical manifestations. Despite earlier diagnoses occurring in most patients, nutritional deficiencies, weight deficits, pancreatic dysfunction, steatorrhea, and meconium ileus remain common for patients with CF during the newborn period. (5)(6) Timely recognition and intervention are critical, as early therapies and outcomes in CF have been shown to have profound long-term effects on nutritional and pulmonary health. (7)(8)(9) Early exposure to antibiotics and other medications may also have long-term negative implications on a patient's health. It is, therefore, necessary that neonatologists be able to recognize and appropriately manage the early clinical manifestations of CF.

## GASTROINTESTINAL MANIFESTATIONS

### Gastroesophageal Reflux Disease

Gastroesophageal reflux (GER) is a common physiologic condition characterized by passive retrograde flow of gastric contents into the esophagus that affects more than 50% of infants. Typically, GER does not require any intervention and resolves by ~1 year of age. This clinical course is similar in patients with CF and GER. Gastroesophageal reflux disease (GERD) occurs when complications of GER occur, such as respiratory compromise or esophagitis. (10) The incidence of GERD in infants with CF is ~25%. (11)(12) The most frequent clinical manifestations of GERD in patients with CF are emesis and possetting, followed by parental-perceived irritability in the infant. However, it is important

to note that these are common symptoms in the newborn period and have been shown to have a poor positive predictive value for GERD in infants with CF. (12) Although GERD has been shown to be associated with worse pulmonary outcomes in older patients, (13) respiratory manifestations of GERD in infancy are rare and typically are limited to wheezing. Failure to thrive has not been associated with GERD in infants with CF. (12)

The evaluation of potential GERD in infants with CF is not different than that in the general population. During the newborn period, it is important to evaluate for any anatomical abnormalities that could be contributing to GERD and would require surgical intervention. An upper gastrointestinal fluoroscopy series is the preferred imaging modality and allows for the evaluation of esophageal abnormalities, hiatal hernias, malrotation, and other anatomical abnormalities of the upper gastrointestinal tract. (10) Although an upper gastrointestinal fluoroscopy series is helpful to diagnose anatomical abnormalities, it cannot diagnose GERD. Radiotracer may be seen infrequently in the lungs, and careful interpretation is required to determine whether this finding is due to primary aspiration, due to aspiration of refluxed contents, or of no clinical significance. Combined multichannel intraluminal impedance and pH measurement (MII-pH) is the preferred test in the evaluation and diagnosis of GERD, having been shown to be superior to other common investigations, including 24-hour pH testing, barium meal, pepsin assay, and even esophagogastroduodenoscopy (EGD). (14) MII-pH may be performed with or without an EGD, with both evaluations typically reserved for patients who do not respond to baseline empirical therapy. If MII-pH is being considered, it is strongly urged that a gastroenterology consultation is obtained to assist in the decision making regarding whether to pair with EGD, timing of MII-pH, and interpretation of results.

Similar to the evaluation of GER and GERD, the management of these conditions in infants with CF is similar to that of the general population. As per the American Academy of Pediatrics (AAP) guidelines, younger infants may benefit from an upright position after feeding, whereas the benefit of side positioning is not as clear. Although placement of an infant in the prone upright position has been theorized to help decrease reflux events in infants, it is critical to remember the associated increased risk of sudden infant death syndrome in infants placed in this position. This position might be preferred if the provider believes that the risk of death from GERD is greater than the risk of sudden infant death syndrome. (15)

Postural draining and percussion is another positional consideration in patients with CF. This technique is performed

on infants and children from the time of diagnosis until they can actively participate in their own pulmonary treatments. This method helps to move mucus out of the lungs, but it has been associated with an increased risk of GER. Two approaches have been studied: the standard 15° to 40° head-down tilt versus the 15° to 30° head-up tilt. Although limited evidence exists, there may be some benefit with a 30° head-up tilt approach because it might decrease the number of GER events, especially those that reach the upper esophagus. (16) Additional noninvasive and nonpharmacologic strategies to treat GER and GERD should likewise follow the previously referenced AAP guidelines. (15)

Pharmacologic management, which focuses on acid suppression, should be reserved for infants with GERD. Although histamine-2 receptor antagonists (H<sub>2</sub>RAs) are a reasonable first choice, proton pump inhibitors (PPIs) are typically preferred owing to superior efficacy and as adjunct therapy with pancreatic enzyme replacement therapy (PERT) to potentially improve nutritional status. (17)(18) These medications may be used empirically for suspected GERD in infants, but other pharmacologic interventions (eg, prokinetics) and more invasive therapies (eg, fundoplication) should be considered only in patients with extremely severe GERD and in consultation with a gastroenterologist. Although fundoplication may potentially help to protect the patient from aspiration, it has significant potential comorbidities (eg, gas, bloating, retching, and dumping); nearly 50% of patients will develop GERD symptoms after fundoplication. (10) It is reasonable to infer that this risk is likely greater if fundoplication is performed during infancy.

The use of PPIs for infants with GER and GERD has become commonplace, with the 2016 CF Registry reporting that more than 50% of patients with CF were prescribed a PPI during the calendar year. (19) This is despite evidence showing that PPI use is significantly associated with an increased number of hospitalizations for pulmonary exacerbations, as well as a small risk of developing hypocalcemia, hypomagnesium, osteopenia, and *Clostridium difficile*. (17)(20) It is not clear whether these associations are causative, simply reflect worse disease, or a combination of both. In addition, prolonged acid suppression with either H<sub>2</sub>RAs or PPIs has been associated with the development of small intestinal bacterial overgrowth (SIBO). (21) With these long-term CF-specific associations established, combined with the known increased risk for the development of necrotizing enterocolitis and late infections in all infants receiving acid suppression medications, cautious consideration should be practiced before prescribing infants with CF either H<sub>2</sub>RAs or PPIs. If H<sub>2</sub>RAs or PPIs are initiated, they should not be considered long-term medications, and providers should

frequently assess whether they need to be continued and weaned once clinically appropriate.

### Dysbiosis

A variety of gastrointestinal manifestations of CF are believed to predispose this population to dysbiosis and SIBO, including delayed intestinal transit time, frequent antibiotic exposure, prolonged use of acid suppression medications, pancreatic insufficiency, intestinal inflammation, and high rates of constipation. (21) A difference in intestinal bacterial composition and lack of diversity has been well-established in patients with CF but was largely felt to develop over the course of a patient's life. Recent data, though, suggest that CFTR dysfunction affects the near sterile gut at birth and influences the acquisition of the gut microbiome, with stool samples as early as 15 days of age showing altered composition compared with controls. (22) Specific findings include expansion of *Escherichia coli*, increased *Enterococcus* species, decreased *Clostridiales* species, and an overall decrease in alpha diversity.

There is no evidence to support a protocol to treat or prevent dysbiosis and/or SIBO in infants with SIBO. Breast-feeding has been shown to improve microbial diversity in the respiratory and intestinal tracts in samples taken from infants with CF from birth through 34 months of age. Furthermore, in the same cohort, improved intestinal, but not respiratory, microbial diversity was associated with longer time until both the first pulmonary exacerbation and initial colonization with *Pseudomonas aeruginosa*. (23) Although longer-term follow-up is required to understand the true impact of early dysbiosis on the health of patients with CF, we strongly encourage providers caring for infants with CF to be mindful of the possible implications of unnecessary exposure to antibiotics and/or acid suppression medications during this time of their life and to ensure that an adequate indication is present before initiating these medications.

### Intussusception

Symptomatic intussusception is a rare manifestation of CF, affecting ~1% of patients. There is a male predominance (2:1) and a bimodal distribution, which includes an initial peak in infancy, with the second peak occurring at approximately 10 years of age. (24) Presentation in infancy typically includes colicky pain/discomfort, vomiting, and, rarely, bloody stools. (25) Diagnosis is typically made by ultrasonography, although air and contrast enema can be both diagnostic and therapeutic, if clinically suspected. Surgery to manually reduce and assess for a potential lead point or



lesion is rarely required but should be considered if contrast enema fails to resolve the intussusception. (24)

### Meconium Ileus

Meconium ileus is an intestinal obstruction caused by thick, adhesive meconium that typically involves the terminal ileum and is most often associated with CF, occurring in 12.5% to 25.9% of newborns with CF, depending on genotype. (19) Meconium ileus initially develops in utero and is frequently the first clinical manifestation of CF.

Both CFTR and non-CFTR genetic factors are thought to contribute to the pathophysiology of meconium ileus, supported by epidemiologic studies and animal models. Meconium ileus is more common in those with class I-III CFTR mutations, which are typically associated with lower CFTR function. (19) Abnormal CFTR protein in the small intestine results in diminished bicarbonate and chloride excretion, which is needed to promote water secretion. (26) With loss of CFTR function, an acidic and dehydrated luminal environment ensues, and the resultant compacted, viscous mucus and other factors combine to form abnormally sticky and tenacious meconium that occludes the intestinal lumen. (3)(4)(27)

Approximately 3% of patients affected by meconium ileus are identified prenatally. (28) Antenatal ultrasonography may identify hyperechoic masses, corresponding to inspissated meconium; this is in contrast to normal fetal meconium, which generally appears more hypoechoic or isoechoic to adjacent bone or liver. (3) A hyperechoic bowel is associated with both meconium ileus and CF but is a nonspecific finding with a broad differential diagnosis that includes normal variant. (29)(30) Other potential sonographic findings of meconium ileus include peritoneal calcifications, dilated bowel proximal to the obstruction, and polyhydramnios. (29)(31)

Algorithms have been developed to guide assessment of fetal risk for CF and meconium ileus after detection of hyperechoic bowel. Parental carrier status should ideally be assessed, with genetic counseling offered thereafter, regardless of outcome, given the limitations of testing and other diseases or syndromes associated with echogenic bowel. (31) Because the finding often subsequently resolves, antenatal ultrasonography should be repeated at least every 6 weeks. (3)(30) Referral to a perinatologist is recommended for coordination of multidisciplinary care around delivery should the findings persist, with access to a center with an experienced NICU team and specialist support, including pediatric surgery. (31)

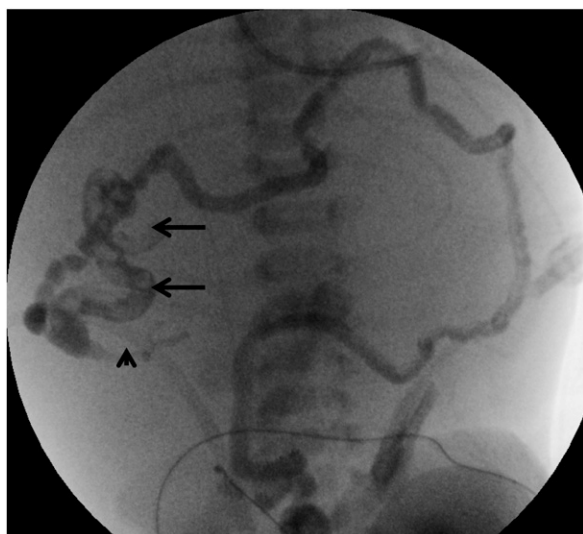
Newborns with meconium ileus typically have symptoms within the first 48 hours after birth; these symptoms vary

depending on the presence or absence of complications. (21) In simple, or uncomplicated, meconium ileus, luminal obstruction by inspissated meconium may occur anywhere from the distal ileum to the proximal colon, leading to proximal bowel distention by additional viscid meconium, gas, and fluid. The distal, unused colon is frequently small in caliber (termed *microcolon*). This leads to nonspecific signs and symptoms of lower gastrointestinal tract obstruction, which may include bilious vomiting, abdominal distention, or failure to pass meconium. (28) Approximately 50% of cases are complicated by segmental volvulus, intestinal atresia, ischemic necrosis, or perforation. Rarely, perforation can lead to pseudocyst formation from encapsulation of meconium into an intestinal membrane. This can lead to meconium peritonitis or giant meconium pseudocyst formation. (24)

Initial management of newborns with meconium ileus is similar to treatment of patients with a suspected small-bowel obstruction. This includes nil per os status, adequate intravenous access, evaluation for an infection, and placement of a nasogastric tube. An abdominal radiograph is the typical first imaging choice and often shows dilated loops of bowel with or without air-fluid levels. In addition, the presence of air in the rectum may vary depending on the “completeness” of the obstruction. The radiograph may show the classic soap bubble sign in the distal small intestine, attributed to meconium that is mixed with swallowed air, and abdominal calcifications as a result of an intrauterine intestinal perforation. (31)

In stable newborns, a contrast enema may be beneficial to detect a microcolon and exclude other anatomical abnormalities, as well as help determine whether surgical intervention is required (Fig 1). The success of medical management with hyperosmolar enemas performed under fluoroscopic guidance to ensure penetration to the terminal ileum has been reported to be 30% to 80%. Although perforation rates of 3% to 23% have been reported with contrast enemas, the goal remains to avoid surgery unless medical management is unsuccessful or the patient has a distended abdomen and peritoneal signs consistent with complex meconium ileus. (31) An algorithm for the treatment of meconium ileus is shown in Fig 2.

In patients with meconium ileus who have not yet been diagnosed as having CF, a full diagnostic assessment should be performed, including serum immunoreactive trypsinogen (if newborn screen has not been performed), as well as a sweat chloride test. A sweat chloride test may be performed 48 hours after birth in term infants assuming that the patient is well hydrated and not edematous. It is



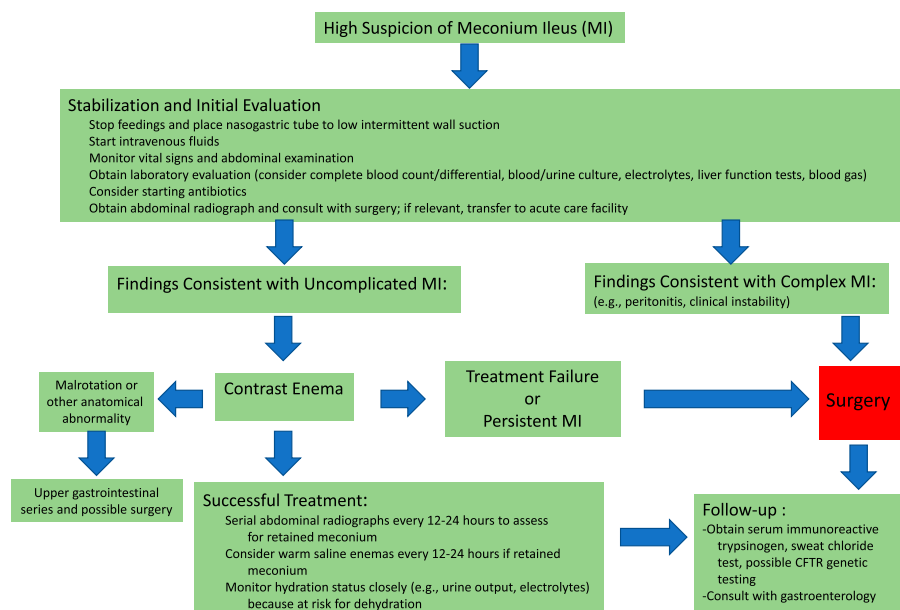
**Figure 1.** Barium enema in a 2-year-old boy diagnosed as having cystic fibrosis showing filling defects of the terminal ileum (arrows) distal to the appendix (arrowhead) with prominent microcolon diagnostic of meconium ileus.

important to know that false-negative serum immunoreactive trypsinogen results have been reported in infants with CF and meconium ileus and does not exclude the diagnosis. (32) In patients unable to have a sweat test performed or in whom confirmatory diagnosis is sought, CFTR genetic testing should be performed from an accredited laboratory. For patients with meconium ileus and known CF, pancreatic insufficiency should be presumed and the patient started on

PERT unless a fecal elastase level is reported as normal (see the Pancreatic Insufficiency section later herein). (33)

For patients requiring surgical correction of the meconium ileus, there are 2 surgical choices, both of which require close postoperative management. An enterotomy with washout and primary anastomosis may be considered and has the benefit of potentially preventing subsequent surgery. However, it has been associated with a high 30% postoperative complication rate. (34) As such, many providers prefer the creation of an ostomy (such as a Bishop-Koop or Santulli) to prevent re-accumulation of stool and allow for bowel irrigation, if needed. Ostomies, though, especially if proximal, risk excessive water and salt loss, which may have a negative influence on the patient's short- and long-term nutritional status and must be monitored closely. (35) A total body deficit of sodium can occur, which may lead to metabolic acidosis and poor weight gain. Total body sodium level can be monitored by measuring a spot urine sodium/creatinine ratio (goal for adequate growth is ratio of 17:52) or a spot urine sodium amount; the patient should be started on sodium supplements if either value is low. (36) Both surgical approaches are associated with a risk of adhesions and increased risk of distal intestinal obstruction syndrome, both of which may also impair long-term intestinal motility. (35)

As soon as clinically indicated, enteral nutrition should be resumed in patients with simple or complex meconium ileus. If total parenteral nutrition is required, an anti-



**Figure 2.** Treatment algorithm for meconium ileus. (Derived from Sathe M, Houwen R. Meconium ileus in cystic fibrosis. *J Cyst Fibros*. 2017;16(suppl 2): S32–S39.)

inflammatory lipid choice should be considered, including medium-chain triglycerides and fish oils to decrease the risk of cholestasis. In Europe, Smoflipid® (Fresenius Kabi USA LLC, Lake Zurich, IL) has routinely been used in affected patients, but it has not routinely been used in the United States for this indication. (31)

### Rectal Prolapse

Cystic fibrosis has been commonly associated with rectal prolapse, with historical data suggesting that approximately 23% of patients with CF experience rectal prolapse. (37) Not surprisingly, with widespread use and expansion of newborn screening for CF, rectal prolapse as a manifestation of the disease has decreased in incidence and was more recently estimated to be as low as 3.5%. (38) Rectal prolapse typically occurs during the toddler years, but it has been described as an early and initial presentation of CF within the first week of life, although its incidence in the neonatal period is not definitively known. (39)(40) Given the very low incidence of rectal prolapse as an initial manifestation of CF, early rectal prolapse should prompt an initial evaluation for other potential etiologies, such as anorectal abnormalities or Hirschsprung disease. (41) We recommend obtaining a sweat test to further evaluate for CF only if the patient has recurrent prolapse or if the prolapse is associated with loose, diarrheal stools (suggesting pancreatic insufficiency).

It is expected that 75% of patients with CF and rectal prolapse will respond to PERT, with full resolution of the prolapse episodes. (39) For patients not responding to PERT in the newborn period, a period of observation with appropriate constipation management would be advised because most patients will eventually outgrow this disorder. Invasive measures such as surgery or sclerotherapy would only be considered in the neonatal period for complex cases in which manual reduction was not possible and/or could lead to other complications (eg, incarceration). (41)

## PANCREATIC AND NUTRITIONAL MANIFESTATIONS

### Pancreatic Insufficiency

The pancreas is one of the earliest and most frequently affected organs in CF, with significant initial injury occurring in utero and initial insult seen as early as 17 weeks' gestation. (42) It is commonly believed that impaired chloride and bicarbonate transport results in pancreatic secretions, which have a lower pH, increased viscosity, and higher protein concentration, altering zymogen secretion and leading to ductal obstruction. (43) Early pancreatic histopathology shows sparing of the islets of Langerhans, and, thus, endocrine

function is not expected during infancy, with onset of CF-related diabetes typically seen later in life. However, acinar plugging with inflammation, ductal injury, and adipose replacement of the pancreatic parenchyma result in pancreatic insufficiency, most notably in patients with class I-III mutations. (44) As such, ~60% of newborns with CF will have pancreatic insufficiency, with another 30% developing pancreatic insufficiency during the next 36 months. (45)

The impact of pancreatic insufficiency on nutrition in infants with CF is profound and cannot be understated. PERT treatment in patients with pancreatic insufficiency is lifelong and must be closely monitored, as described later herein. In infants with CF who are receiving adequate PERT dosing but continue to experience symptoms of pancreatic insufficiency, such as bloating, steatorrhea, diarrhea, and weight loss, alternative etiologies should be considered and evaluated for, including, but not limited to, SIBO, short bowel, and cholestasis.

### Nutrition

Poor nutrition should be an ever-present concern among providers caring for patients with CF. The known combination of increased energy losses, increased resting energy expenditure, and inadequate nutritional intake are known difficulties that increase the risk of undernutrition. The extent to which these affect infants with CF is unclear. However, it is well-established that in infants with CF, poor early nutritional status that is left untreated is associated with stunted growth, impaired cognitive function, worse lung function, and poor survival. (46)

Goal nutrition specifically for infants with CF is not well-studied, but the general principles are thought to be similar to those for toddlers and children with CF. The resting energy expenditure of patients with CF is greater than that of healthy same-age children, and it is assumed to be similar among infants. Therefore, goal intake should be 110% to 200% of that expected for the healthy same-age population. Close monitoring of growth parameters should be conducted with a goal of achieving and maintaining a weight-for-length at the 50th percentile (0 SD) as healthy same-age infants on the sex-appropriate World Health Organization (WHO) growth curve. (47) It has been recommended that head circumference, weight, length, and weight-for-length all be measured a minimum of 1 to 2 times per week until the child is thriving. (48) Although protein-energy malnutrition has been described in infants with CF, (49) this is largely historical, or more prevalent in developing countries, and is unlikely to be a concern if caloric goal intake is achieved.

Human milk remains the preferred source of nutrition in infants with CF. The benefits of human milk in the general population is well known, and it may be even more important for patients with CF. Infants with CF who receive human milk as their nutritional source have been shown to have improved microbial diversity of the intestinal and respiratory tracts, longer time until their first pulmonary exacerbation, longer time to colonization with *Pseudomonas aeruginosa*, reduction in decline of pulmonary function as measured by forced expiratory effort in 1 second, and decreased number of pulmonary infections during the first 3 years after birth. (23)(50)(51) If human milk is unavailable, standard formula is the preferred alternative. Despite the high frequency of pancreatic insufficiency, formulas containing higher concentrations of medium-chain triglycerides have shown no benefit, assuming adequate PERT is provided.

It is critical to ensure adequate PERT in pancreatic-insufficient patients with CF. It is well-established that ~60% of newborns with CF will have pancreatic insufficiency, with another 30% developing it during the next 36 months, predominantly those with class I-III mutations. (45) Pancreatic status should be evaluated by obtaining a fecal elastase level in all infants with CF and at least 1 mutation known to be associated with pancreatic insufficiency, or if inadequate growth/nutrition occurs. Patients with a fecal elastase level less than 200 µg/g should be considered to have pancreatic insufficiency and should receive PERT. Note that fecal elastase may vary in the first year after birth in infants with CF, and those with levels between 50 and 200 µg/g should be reevaluated at 1 year of age. Recommended PERT dosing is shown in the Table. Of note, in a cohort of 205 infants with CF and pancreatic insufficiency, higher PERT dosing was not associated with improved growth parameters, but patients receiving PERT + PPIs achieved greater weight z scores than those receiving PERT + H<sub>2</sub>RAs. (18)

Fat-soluble vitamin deficiencies are common in patients with CF and pancreatic insufficiency, occurring in up to 35% of these children. Vitamin D has specifically been evaluated in infants and has been reported to be deficient in 22% of patients. (47) Guidelines outlining when to assess fat-soluble vitamin levels do not yet exist, but initial dosing and goal levels are shown in the Table. For patients who experienced a prolonged nursery or NICU admission, we recommend assessment of vitamin D level at least monthly until thriving, and then every 3 months.

Infants with CF are at increased risk for salt loss due to excessive sweating, intestinal malabsorption (especially if an ostomy is present), and chronic inflammation. Excessive salt

loss has been associated with impaired growth in infants with CF. Likewise, zinc deficiencies have been reported in infants with CF and are associated with growth problems, increased susceptibility to infection, and ocular concerns. (47) As such, sodium and zinc supplementation is often considered in at-risk patients, with dosing guidelines shown in the Table. Currently, a monitoring protocol for sodium and zinc deficiencies does not exist. As such, the provider must maintain a high index of suspicion and monitor levels as clinically indicated.

The widespread and expanded use of newborn screening for CF has resulted in earlier diagnosis of CF and significantly improved nutritional outcomes. However, although weight and weight-for-length measures are improving, linear stunting remains a concern. (5)(51) Furthermore, there are some infants who simply cannot tolerate the increased caloric demand by mouth. In cases where it is believed that a patient cannot consume an adequate amount of calories by mouth to meet and improve on age-dependent anthropometric and growth targets despite an appropriate evaluation, enteral tube feeding should be recommended. In patients in whom less than 3 months of tube feedings are expected, nasogastric tube placement is appropriate, with nasojejunal reserved only for those who cannot tolerate nasogastric feedings. When considering the placement of an enteral feeding tube in an infant with CF, a thorough GER evaluation should be performed (preferably with the assistance of a gastroenterologist). There is no specific method or route of delivery for PERT that is recommended during tube feeding, although continuous feedings at night are preferred. Even if surgical placement of an enteral tube is performed, airway clearance may resume 24 hours after placement. (52)

## HEPATOBIILIARY INVOLVEMENT

### Neonatal Cholestasis

Cholestasis is the earliest and most common neonatal manifestation of liver involvement in patients with CF, often recognized by elevated serum conjugated/direct bilirubin levels greater than 1.0 mg/dL (>17 µmol/L). Its incidence in infants diagnosed as having CF in a statewide newborn screening program is considered low at ~6% but is ~140-fold greater than that in the general population of term infants. (53)(54) Patients with complicated meconium ileus are at increased risk for cholestasis, with an incidence greater than 25% in this group. (54)

In addition to jaundice, other clinical features of CF-associated neonatal cholestasis are often nonspecific. Affected

**TABLE. General Nutritional Guidelines for Infants with Cystic Fibrosis**

Growth target	Weight-for-length at 50th percentile (0 SD) for healthy same-age population
Route of nutrition	By mouth as tolerated Enteral tube to be considered if unable to tolerate caloric demands by mouth
Preferred nutrition	Human milk (standard formula if human milk not available)
Energy target	110%–200% expected energy requirements for same-age healthy infant
Pancreatic status assessment	Fecal elastase performed in any patient with $\geq 1$ cystic fibrosis–causing mutation associated with pancreatic insufficiency or if inadequate growth/nutritional status occurs
PERT dose (if pancreatic insufficient)	2,000–4,000 U of lipase/120 mL of human milk or formula or $\sim 2,000$ U of lipase/1 g of dietary fat
Vitamin A dose	No specific dose but should be a component of a fat-soluble multivitamin provided
Vitamin D dose (as vitamin D <sub>3</sub> )	400 IU/d (maximum 1,000 IU/d if deficient) until age 1 y Goal is minimum serum 25-hydroxyvitamin D level of 20 ng/mL (50 nmol/L)
Vitamin E dose (as $\alpha$ -tocopherol)	50 IU/d until age 1 y; goal is plasma $\alpha$ -tocopherol/cholesterol ratio $>5.4$ mg/g
Vitamin K <sub>1</sub> dose	0.3–1 mg/d
Sodium supplementation	1–2 mmol/kg per day for breastfed infants aged 0–6 mo at risk for sodium deficiency; give in small portions throughout the day in dilute water or fruit juice  Up to 4 mmol/kg per day may be considered in infants with special needs (eg, living in hot ambient temperatures, increased fluid losses, or ostomy present)
Zinc dose	1 mg/kg per day (maximum 15 mg per day) until age 2 y

PERT=pancreatic enzyme replacement therapy.

Summarized from Wilschanski M, Braegger CP, Colombo C, et al. Highlights of the ESPEN-ESPGHAN-ECFS Guidelines on Nutrition Care for Infants and Children With Cystic Fibrosis. *J Pediatr Gastroenterol Nutr.* 2016;63(6):671–675.

infants may have acholic stools, hepatomegaly, splenomegaly, hypoalbuminemia, and/or elevated serum transaminase, alkaline phosphatase, and/or  $\gamma$ -glutamyl transferase (GGT) levels. (55)(56)

The pathogenesis of neonatal cholestasis in CF is not well-defined, but the predominant mechanism is likely related to intraluminal bile stasis in a pattern similar to that seen in the lungs, intestine, and pancreas. CFTR is expressed in cholangiocytes (not hepatocytes), which contribute up to 40% of bile. Defective cholangiocyte chloride and bicarbonate transport results in decreased bile flow and abnormally thickened secretions, leading to bile duct plugging. Autopsy and biopsy specimens may demonstrate excess, inspissated mucus in the biliary tract with focal or diffuse plugging. (56)(57) In most cases, portal tract expansion and ductular proliferation are noted, in keeping with extrahepatic biliary obstruction, and at times is indistinguishable from biliary atresia. (55)(57)(58)

In infants with CF and cholestasis, a targeted evaluation with consideration of other etiologies is still recommended, often in concert with a pediatric gastroenterologist/

hepatologist. Biliary atresia, in particular, must be considered in the presence of acholic stools, especially because contracted or absent gallbladders may occur in infants with CF as well. Conversely, term neonates with unexplained cholestasis should be evaluated for CF as part of a full evaluation. (53)(58)

In a retrospective cohort study, cholestasis in patients with CF was largely diagnosed within the first 2 months after birth, with total serum bilirubin levels peaking within the first 3 months after birth in all patients. The diagnosis and peak bilirubin level occurred significantly earlier in those with a history of meconium ileus. (54) Although cholestasis should generally resolve within the first year after birth with no sequelae, in some patients it may persist up to 5 years, and reported cases of liver failure and death are rare. (54)(55)(56) Patients with CF and early cholestasis generally have a favorable clinical course, whereas the long-term impact of early meconium ileus or cholestasis on CF-associated liver disease remains unclear.

Management of cholestasis is considered mostly supportive, warranting close monitoring of growth and fat-soluble

vitamin status. Ursodeoxycholic acid treatment may benefit patients with neonatal cholestasis, but there is insufficient evidence to justify its routine use in all infants with CF. (54)(55)(56)

### Hepatic Steatosis

Hepatic steatosis is a common hepatic finding in CF at any age, with a reported prevalence of 23% to 70%, although no specific neonatal data are available. (50)(59) It has often been associated with long-term malnutrition or deficiencies of a trace element or minerals (eg, choline, carnitine, essential fatty acids); however, this is not always the case, so this finding could also be secondary to CFTR dysfunction. (50) Although hepatic steatosis may be seen in the neonatal period of patients with CF, its incidence would be expected to be quite rare and clinical implications minimal. As such, findings suggestive of steatosis on neonatal ultrasonography (such as homogenous hyperechogenicity) should prompt a broad evaluation that may include CF, but not as the primary focus.

### Liver Enzyme Elevations

Elevated liver enzyme levels are common during childhood in patients with CF diagnosed predominantly by newborn screening. Approximately 90% of patients will have at least 1 serum elevation of aspartate aminotransferase (AST) or alanine aminotransferase levels, and ~40% will have at least 1 serum elevation of GGT levels during childhood. Such elevations are particularly common in the first 2 years after birth, even at health supervision visits. Liver enzyme elevations are typically mild; elevations that are greater than 3 times the upper limit of normal (ULN) are rare at any age in patients with CF and occur more commonly in children younger than 24 months and during intercurrent illnesses. (60)

Intermittent elevations of transaminase levels do not seem to predict progression to cirrhosis, whereas persistent (>6 months) elevations in AST or GGT levels greater than  $1.5 \times$  ULN have been associated with progression to clinically significant liver disease. (60)(61) In patients with a long NICU course or early hospital admission and elevated AST, alanine aminotransferase, and/or GGT levels, routine monitoring is encouraged. This should include a hepatic function panel that includes GGT every 1 to 2 weeks if clinically stable, or as clinically indicated otherwise. Levels that are  $3 \times$  ULN or higher, persistent elevation, or any suggestion of progression of disease should prompt consultation with an experienced gastroenterologist or hepatologist.

### Gallbladder and Biliary Tract Involvement

Gallbladder abnormalities have been observed in 25% to 50% of patients with CF, most of which are incidentally

found on imaging. (62) Of particular importance in the neonate is the finding of a micro-gallbladder. Although it is benign and does not require treatment, it can mimic the ultrasonography findings in biliary atresia, which may raise diagnostic uncertainty if there is concurrent cholestasis.

Gallstones are more frequent in pediatric CF populations, with a reported pediatric incidence of 3% to 25%, and has been reported in the neonatal period. (62)(63) It is unclear why these patients with CF are predisposed to gallstone formation, but gallstones are more likely to be pigmented and are unlikely to dissolve after ursodeoxycholic acid treatment. Pathogenesis is likely multifactorial, possibly related to cholestasis, gallbladder hypokinesia, increased calcium-mucin binding, lower biliary pH, and/or increased enterohepatic circulation leading to hyperbilirubinemia. Recommended treatment of symptomatic cholelithiasis in patients with CF is generally similar to that in the general population. (64)

### SUMMARY

- Based on evidence level A, gastrointestinal, pancreatic, and hepatic signs and symptoms are the most common initial manifestations in infants with cystic fibrosis (CF).
- Based on evidence level C, the decision to treat patients with CF and gastroesophageal reflux disease must be balanced between short-term effect on disease and nutrition with potential long-term consequences of dysbiosis and worse pulmonary outcomes.
- Based on evidence level C, early recognition of meconium ileus is critical, and management should follow an evidence-based algorithm. For those who require surgical intervention, close attention must be given to nutrition, hydration, and sodium status.
- Based on evidence level A, early nutrition is critical for patients with CF and can significantly affect long-term pulmonary, gastrointestinal, morbidity, and mortality outcomes.
- Based on evidence level B, the nutritional goal for all patients with CF is to achieve a weight-for-length at the 50th percentile (0 SD), similar to healthy same-age infants.
- Based on evidence level B, human milk is the preferred source of nutrition for infants with CF. If human milk is not an option, standard formula is appropriate.
- Based on evidence level B, early hepatic and gallbladder findings are not uncommon and typically do not require intervention.



## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the caloric requirements for optimal postnatal growth of preterm and term infants, accounting for caloric expenditures needed for physical activity and maintenance of body temperature.
- Know the causes, clinical manifestations, diagnosis, and management of congenital or acquired malabsorption syndromes.
- Know the clinical manifestations and pathophysiology of cystic fibrosis in the newborn infant.
- Know the diagnosis and management of cystic fibrosis in newborn infants.

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1. A female infant born at term is diagnosed as having cystic fibrosis (CF) after newborn screening. At 2 months of age she presents with colic, discomfort, and vomiting. Intussusception is suspected. Which of the following statements regarding intussusception and CF is correct?
  - A. Surgery is the first line of treatment.
  - B. It is more common in female infants compared with males.
  - C. There is a peak occurrence in infancy, with a second peak occurring at approximately 10 years of age.
  - D. Intussusception will occur in more than 10% of patients with CF during childhood.
  - E. The optimal diagnostic test is magnetic resonance imaging.
2. Prenatal ultrasonography identifies hyperechoic mass, peritoneal calcifications, and polyhydramnios. Meconium ileus is suspected. Which of the following statements about meconium ileus is correct?
  - A. Meconium ileus initially develops in utero and is frequently the first clinical manifestation of CF.
  - B. Meconium ileus is less common in those who have class I-III CF transmembrane regulator mutations.
  - C. Hyperechoic bowel is a highly sensitive and specific sign for the diagnosis of CF.
  - D. The finding of meconium ileus should lead to prompt delivery of the infant, with antenatal steroids administered before delivery if gestational age is before 34 weeks.
  - E. Newborns with meconium ileus typically have symptoms within the first 2 hours after birth, such as respiratory distress or bilious emesis.
3. A term newborn male infant presents with rectal prolapse. The physical examination findings are otherwise normal. Before the event, the infant had been breastfeeding well and having normal-appearing stools for his age. Which of the following is an appropriate next step for this patient?
  - A. Sweat chloride test.
  - B. Surgical repair under general anesthesia.
  - C. Sclerotherapy.
  - D. Evaluation for etiologies such as anorectal malformation or Hirschsprung disease.
  - E. Sepsis evaluation and broad spectrum intravenous antibiotic therapy.
4. A 5-month-old boy has been diagnosed as having CF, with a history of meconium ileus, relatively severe gastroesophageal reflux, and frequent diarrhea. Which of the following statements regarding pancreatic insufficiency in CF is correct?
  - A. The earliest potential manifestation and injury occurring from pancreatic insufficiency is with the addition of nonmilk foods.
  - B. Approximately 30% of infants with CF will have pancreatic insufficiency by the time they reach the teenage years.
  - C. Pancreatic acinar plugging with inflammation, ductal injury, and adipose replacement of the pancreatic parenchyma result in pancreatic insufficiency, most notably in patients with class I-III mutations.
  - D. Treatment with pancreatic enzyme replacement therapy should be withheld until the infant reaches 6 months of age, and then given in short intervals of 1 to 2 weeks, to avoid complications of liver and renal dysfunction.
  - E. In most patients with CF, pancreatic injury leading to diabetes will precede pancreatic insufficiency leading to gastrointestinal symptoms.

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5. A term male infant who had meconium ileus complicated by meconium peritonitis and required surgical intervention for bowel obstruction has been diagnosed as having CF. He is recovering from surgery, and nutrition is being advanced. Which of the following statements regarding nutrition for infants with CF is correct?
- A. The preferred source of nutrition in infants identified as having CF is elemental formula.
  - B. Several meta-analyses have shown that the addition of probiotics, such as *Lactobacillus* and *Bifidobacterium*, during infancy is preventive for *Pseudomonas* respiratory infections in childhood.
  - C. The caloric intake and expenditure of infants with CF is assumed to be the same as that of similar-age infants without CF.
  - D. Fat-soluble vitamin deficiencies are common in patients with CF, particularly vitamin D.
  - E. It has been well established that formulas containing higher concentrations of medium-chain triglycerides are beneficial for both gastrointestinal and respiratory symptoms, with improved growth outcomes.

# Gastrointestinal, Pancreatic, and Hepatic Manifestations of Cystic Fibrosis in the Newborn

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# Macronutrient Digestion and Absorption in the Preterm Infant

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## Education Gap

Knowledge of the importance of human milk enzymes in macronutrient digestion has increased greatly over recent years, and provides a further impetus to the use of human milk, especially mother's own milk, in the nutrition of preterm infants.

## Abstract

The human fetus receives oral nutrition through swallowed amniotic fluid and this makes a significant nutritional contribution to the fetus. Postnatally, macronutrient absorption and digestion appear to function well in the preterm infant. Although pancreatic function is relatively poor, the newborn infant has several mechanisms to overcome this. These include a range of digestive enzymes in human milk, novel digestive enzymes involved in fat and protein digestion that do not appear to be present in the older child or adult, and the presence of a *Bifidobacterium*-rich colonic microbiome that may "scavenge" unabsorbed macronutrients and make them available to the infant.

**AUTHOR DISCLOSURE** Drs Rogido and Griffin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

BSDL	bile salt-dependent lipase
BSSL	bile salt-stimulated lipase
GLUT2	glucose transporter 2
GLUT5	glucose transporter 5
HMO	human milk oligosaccharide
IMMC	interdigestive migrating motor complex
LCPUFA	long-chain polyunsaturated fatty acid
PEPT1	peptide transporter 1
PLRP2	pancreatic lipase-related protein 2
PTL	pancreatic triglyceride lipase
SGLT1	sodium-glucose linked transporter 1

## Objectives After completing this article, readers should be able to:

1. Understand the importance of human milk in macronutrient digestion in the preterm infant.
2. Understand the role of the colonic microbiome of human milk-fed infants in scavenging unabsorbed nutrient in the preterm infant.
3. Understand the importance of relative pancreatic exocrine insufficiency in preterm infants and the alternative digestive enzymes that serve to mitigate its effect.

## INTRODUCTION

Current nutritional recommendations in the preterm infant emphasize that postnatal growth mirrors that of the fetus of the same gestational age. Typically, this goal is not met and the growth of preterm infants, especially very low-birthweight infants (birthweight <1,500 g), is often far slower than in utero growth. (1) Although there is evidence of some improvement in recent years, (2) these nutritional deficits are associated with poorer long-term neurodevelopmental outcomes. Much of the early growth deficits of preterm infants are associated with reduced protein and energy intake, (3) and both poor growth and lower nutrient intake are associated with poorer outcomes. (2)(3)

Traditionally, neonatologists have some hesitancy when initiating and advancing enteral feedings in very preterm infants because of the perceived associated risk of necrotizing enterocolitis. However, there is good evidence that more conservative approaches to feeding, such as prolonged periods of “trophic” feedings, very slow advancement of enteral feeding volume, and delayed fortification of human milk, are not associated with lower rates of NEC. (4)(5)(6)(7) (8) Studies have found that these cautious regimens may be associated with a number of adverse outcomes such as lower nutrient intakes, (8) prolonged use of central lines, delayed establishment of full enteral feedings, (5)(6)(7) increased risk of infection, (7) poorer growth, (6) and increased length of stay. (5)

Empirically, most preterm infants seem able to adapt well to enteral feedings. Nevertheless, many neonatologists continue to remain apprehensive about feeding very preterm infants as a result of unfounded concerns about NEC and are reluctant to be the initiator of feedings. However, this misconception—that the fetus is entirely parenterally fed (via the umbilical vein) and that newborn infants (term or preterm) receive their first enteral feeding after birth—is actually incorrect.

## ENTERAL NUTRITION OF THE FETUS

Fetal swallowing is first seen at 18 to 20 weeks of gestation and plays an important role in the regulation of amniotic fluid volume. The volume ingested in human fetuses is hard to assess. In fetal sheep, fluid flow along the esophagus is bidirectional, but net inward amniotic fluid flow averages 175 mL/kg per day at 75% of term gestation (30 weeks' gestation in humans) increasing to 274 mL/kg per day at 85% of term gestation (34 weeks' gestation in humans). (9) Both are far higher than the fluid intake of an adult sheep (40–60 mL/kg per day).

Ingestion of amniotic fluid by the fetus has an important *nutritional* role. There is good evidence that esophageal atresia (which prevents fetal swallowing) reduces birthweight. Birthweight Z score is lower in infants with esophageal atresia than in infants with anorectal malformations. (10) Although infants with proximal intestinal obstructions (both esophageal atresia and duodenal atresia) have associated reduced birthweight Z scores, infants with a more distal obstruction (jejunal atresia and ileal atresia) have appropriate fetal growth. Esophageal ligation in fetal rabbits leads to significant reductions in birthweight and birth length compared with sham operations, and these effects are reversed by esophageal infusions that restore fetal “swallowing.” (11) Based on these studies, investigators estimated that swallowed amniotic fluid provides 10% to 14% of nutrition in the fetal rabbit. (11)

## Amino Acids in Amniotic Fluid

Human amniotic fluid contains a broad range of amino acids; concentrations of alanine, lysine, and phenylalanine are high, whereas that of cysteine is low. (12) The amount of amino acids in amniotic fluid is equivalent to a protein content of approximately 0.4 g/dL (4 g/L). Although this amount is less than that found in human milk (typical estimate 1 g/dL [10 g/L]), it could be nutritionally significant if sufficient amniotic fluid is ingested.

Methionine in amniotic fluid is of particular interest. In rodent models, maternal malnutrition leads to reduced amniotic fluid methionine (and phenylalanine) levels, and amniotic methionine is correlated with fetal birthweight. (13) Similar data are reported in humans. In a study of 625 healthy pregnancies, amniotic fluid methionine concentrations between 13 and 17 weeks' gestation were positively associated with birthweight, and amniotic fluid cysteine concentration was negatively associated with birthweight. (14)

## Adaptation of Amniotic Fluid Absorption

Absorption of amniotic fluid components by the fetus seems to be adaptable. In one study, pregnant rabbits received intrauterine infusions of galactose or an inert control for 6 days. Exposure of the fetuses to galactose in the amniotic fluid led to increased galactose and glucose uptake in the proximal and distal small intestine. (15) This suggests that the fetus (and by extension, the preterm infant) may be able to adapt to new dietary components by upregulating the enzymes and transporters required to digest and absorb them.

## Absorption of Macromolecules by the Fetal Gastrointestinal Tract

The fate of proteins in amniotic fluid has been studied in rhesus monkeys. (16) The authors injected an intact protein, labeled with  $^{35}\text{S}$ -methionine, into the amniotic fluid of pregnant rhesus monkeys. The clearance of the protein was largely determined by the rate of fetal swallowing, and evidence of proteolysis of the labeled protein was observed along the length of the small intestine. Amino acids released by proteolysis of the labeled protein were incorporated into gut proteins and released into the fetal plasma as amino acids, where they equilibrated rapidly with maternal amino acids and entered the amniotic fluid amino acid pool. One day after peak  $^{35}\text{S}$ -methionine enrichment of the amniotic amino acid pool occurred,  $^{35}\text{S}$ -methionine-labeled amino acids were detected in the fetal plasma, indicating that amniotic fluid amino acids were being used for protein synthesis. Labeled proteins were also recovered from the fetal lung, liver, skeletal muscle, and brain. The authors estimated that amniotic fluid amino acids contributed 10% to 15% of the nitrogen requirement of the fetus. (16)

## THE ROLE OF HUMAN MILK IN DIGESTION AND ABSORPTION

The ideal milk for all infants, including preterm infants, is human milk, preferably their own mother's milk, or failing that, donor human milk. The main nutritional disadvantages of human milk are the low content of energy, protein, calcium, and phosphate relative to the very high nutritional needs of preterm infants. However, it has some specific nutritional advantages over formula, such as containing many enzymes important for digestion.

### Human Milk Lipase

Early evidence that human milk lipases may be important for fat digestion came from a small randomized trial in the 1980s. Preterm infants fed a preterm formula had significantly higher fecal fat excretions ( $11.9\% \pm 1.4\%$ ) than those fed a 60:40 mixture of preterm formula and fresh human milk ( $4.7\% \pm 0.5\%$ ). (17)

One enzyme that may explain these findings is bile salt-stimulated lipase (BSSL), a lipase found in human milk, and the counterpart of bile salt-dependent lipase (BSDL) secreted by the exocrine pancreas. BSSL completes the final stage of triglyceride digestion by converting monoglycerides (produced by colipase-dependent pancreatic lipase) to free fatty acids. (18) BSSL is not present in formula and is

inactivated by pasteurization of human milk. (19) This may be a possible explanation for fat absorption being 17% lower in preterm infants receiving pasteurized mother's own milk compared with those receiving unpasteurized mother's own milk. (20) Human BSSL is commercially available as a recombinant protein (rhBSSL). Although one small study suggested that addition of rhBSSL to pasteurized human milk or formula improved growth and long-chain polyunsaturated fatty acid (LCPUFA) status, (21) this has not been borne out in a larger trial. (19) Although that larger study found that rhBSSL had no effect on growth of preterm infants ( $n=415$ , gestational age  $\leq 32$  weeks), significant improvements in growth were found in small-for-gestational age preterm infants in a planned subgroup analysis ( $n=62$ ). (19)

### Other Enzymes in Human Milk

Various other enzymes are present in human milk that may potentially play a role in the digestion of lipids, carbohydrates, and proteins (Table). (22)(23)(24) As well as containing "traditional" digestive proteins, human milk contains a number of proteases that usually perform nondigestive functions, but that are able to digest human milk proteins. (24) For example, cathepsin D is usually involved in the degradation of intracellular proteins and the inactivation of growth factors and peptide hormones, but is also able to digest at least 24 proteins found in human milk. (24)

In addition, human milk factors may make otherwise nondigestible human milk components (eg, human milk oligosaccharide [HMO]) bioavailable by modifying the microbiome of the preterm infant (to be described in more detail later in this article).

## CARBOHYDRATE ABSORPTION

### Carbohydrate Digestion/Absorption in Adults

In adults, large carbohydrates are digested in a 2-stage process beginning with salivary  $\alpha$ -amylase, which is inactivated in the acid pH of the stomach, and continuing with pancreatic  $\alpha$ -amylase in the small intestine, resulting in a combination of mono-, di-, and trisaccharide, and dextrans. These in turn are broken down by border enzymes (eg, lactase, sucrase, glucoamylase, and maltase) into monosaccharides, which are absorbed by a combination of facilitated diffusion and active transport (using transporters such as glucose transporter 2 [GLUT2], GLUT5, and sodium-glucose linked transporter 1 [SGLT1]).

In newborn infants, the situation is potentially less complex, with 3 major sources of carbohydrates:

TABLE. Digestive Enzymes Present in Human Milk (22)(23)(24)

MACRONUTRIENT	ENZYME	USUAL ROLE
Lipids (22)(23)	Lipoprotein lipase	Lysis of triglycerides to 2 free fatty acids and a monoglyceride
	Bile salt-stimulated lipase (BSSL)	Lysis of monoglycerides to free fatty acids and glycerol
Carbohydrate (22)(23)	$\alpha$ -amylase (diastase)	Hydrolysis of $\alpha$ -linked polysaccharides at random locations, finally producing glucose, maltose, and maltotriose
	$\beta$ -amylase	Hydrolysis of 1,4-glycosidic bonds to release maltose from the nonreducing end of polysaccharides
Protein (24)	Chymotrypsin	Cleaves peptide bonds adjacent to large hydrophobic amino acids
	Pepsin	Cleaves peptide bonds adjacent to hydrophobic and aromatic amino acids
	Trypsin	Cleaves peptide bonds adjacent to lysine or arginine amino acids (unless followed by proline)
	Cathepsin D	Non-nutritional (but able to cleave $\alpha$ -, $\beta$ -, and $\kappa$ -casein)
	Plasmin	Non-nutritional (but able to cleave $\alpha$ -, $\beta$ -, and $\kappa$ -casein, and mucin-1)
	Elastase	Non-nutritional (but able to cleave $\alpha$ - and $\beta$ -casein)
	Glutamyl endopeptidase	Non-nutritional (but able to cleave some human milk proteins)
	Proline endopeptidase	Non-nutritional (but able to cleave some human milk proteins)

1. Lactose, the dominant carbohydrate in human milk, with a concentration of 5.6 to 7.8 g/dL.
2. A diverse group of HMOs (1.2-2.1 g/dL).
3. Maltodextrins or corn syrup solids, polymers of glucose of varying length linked by 1,4-glycosidic bonds. These are found in preterm infant formulas and in human milk fortifiers.

In addition, human milk contains small amounts of free monosaccharides (typically <0.1 g/dL).

### Lactose

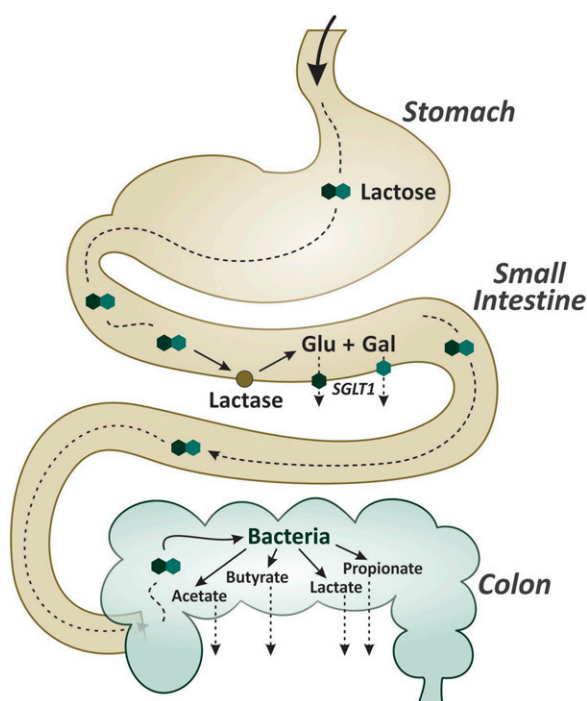
Lactose is the predominant carbohydrate in human milk, and consists of a galactose and glucose joined by  $\beta$ -1,4-glycosidic bonds. It is digested by lactase bound to the brush border membrane of the small intestine.

Lactase is active in the fetus. In the lamb (human gestation equivalent ~32 weeks), intra-amniotic injection of lactose leads to a rapid rise in blood glucose suggesting that lactase and glucose transporters are present in the fetal intestine. (25) In contrast, intra-amniotic injection of sucrose or maltose does not lead to an increase in fetal blood glucose, implying that neither sucrase nor maltase is present in the fetus. (25) In the human fetus, intestinal lactase is detectable in very low levels by 12 weeks of gestation. Levels slowly increase to about 30% of the levels seen in term infants by 34 weeks' gestation and to 70% of term infant levels by 35 to 38 weeks' gestation. (26)

Postnatally, jejunal lactase activity in the piglet increases rapidly after 24 hours of colostrum or milk feedings, but not after feedings with water or after being nil per os. (27)

Lactase activity can be measured indirectly in the preterm infant from the urinary lactose-lactulose ratio. Lactase activity can be detected by 10 days after birth (the earliest time studied by the investigators) and increases at least 3-fold by 28 days after birth. (28) Lactase activity was higher in human milk-fed infants than in formula-fed infants, and lower in infants in whom initiation of feedings was more delayed. (28) Lactase activity was significantly inversely correlated with the time to reach full enteral feedings, which was lower in infants with higher lactase activity. (28) Lactase activity is also higher in infants of higher gestational age. (29)

Lactose absorption is very efficient in the preterm infant with less than 2% of lactose carbons being excreted in the feces, (30) though whether this is the result of hydrolysis by lactase is open to question. (26) The 2 carbons from lactose can be absorbed by 2 separate mechanisms (Fig). The first is lactase dependent, where lactose is digested by lactase in the brush border to galactose and glucose, which are then transported into the enterocyte by SGLT1, and across the basolateral membrane by GLUT2. The second is lactase independent, where undigested lactose undergoes bacterial fermentation in the colon, producing various short-chain fatty acids such as acetate, lactate, propionate, and butyrate, which are absorbed across the colonic mucosa. Preterm infants are known to have high breath hydrogen levels when



**Figure.** Schematic representation of lactose absorption. Lactose can be digested in the small intestine by brush border-bound lactase into glucose and galactose, which are then absorbed via the transporter sodium-glucose linked transporter 1 (SGLT1). Unabsorbed lactose can be fermented in the colon by bacteria into acetate, butyrate, lactate, and propionate which can be absorbed across the colonic mucosa. Less than 2% of lactose carbons are excreted in the stool in preterm infants.

fed lactose, which would be consistent with significant levels of colonic fermentation. It is also possible that unabsorbed glucose and galactose may undergo fermentation in the small bowel. Human colonic bacteria (with or without lactobacilli) have been shown to be able to ferment lactose to acetate, lactate, propionate, and butyrate, (31) and stable isotope studies in preterm infants have demonstrated that they have a high capacity to absorb acetate, which could be sufficient to explain the absorption of a significant proportion of lactose carbon. (32)

Regardless of the balance between the 2 mechanisms, lactose is very well-tolerated by preterm infants without evidence of malabsorption (such as diarrhea or poor growth).

### Oligosaccharides

The concentration of HMOs is high in early lactation but falls as lactation proceeds. (33) Human milk contains more than 100 HMOs. All begin with the lactose linkage of glucose- $\beta$ -1,4-glucose, but a variety of sugars (including galactose, N-acetylglucosamine, fucose, and N-acetylneuraminic acid) are bound to the glucose residue. (33) Humans lack the required enzymes to digest HMOs, so they are resistant

to digestion in the small intestine. (33) Small amounts of intact HMOs are absorbed and may be subsequently excreted in the urine, but the majority of HMOs enter the colon intact. (33)

In the colon, bacteria digest the HMOs and this is a significant contribution to breath hydrogen. (34) Not all bacteria, however, are able to digest HMOs. *Bifidobacterium* (35) and *Bacteroides* species are especially well-suited to digest HMOs. (36) Some biovars of *Bifidobacterium longum* are able to grow well in vitro with HMOs as the sole carbon source. (37) In contrast, other “pathogenic” bacterium such as *Enterococcus*, *Streptococcus*, *Clostridium*, and *Escherichia coli* strains are less able to digest HMOs. (36) It has been suggested that humans and *Bifidobacterium* have coevolved, with humans producing milk that is especially well-suited to support *Bifidobacterium* growth in the colon, in return for the beneficial results of a *Bifidobacterium*-rich colonic microbiota. (37)

The products of bacterial fermentation of HMO—acetate, butyrate, lactate, and propionate—are readily absorbed in the colon, and serve to largely offset the energetic costs of maternal synthesis of HMOs.

### Glucose Polymers

Glucose polymers, often described as maltodextrins or corn syrup solids, are present in infant formulas and in human milk fortifier. They compose a collection of polymers of different length joined by 1,4-glycosidic bonds. These bonds are susceptible to digestion by amylases. There are 4 main sources of amylase in the preterm infant: 1)  $\alpha$ -amylase in human milk; 2)  $\beta$ -amylase in human milk; 3) salivary  $\alpha$ -amylase; 4) pancreatic  $\alpha$ -amylase.

$\alpha$ -amylase randomly hydrolyzes 1,4-glycosidic bonds along the length of the polymer to produce a mixture of glucose, maltose, and maltotriose, whereas  $\beta$ -amylase removes a maltose from the nonreducing end of the polymer.

Both  $\alpha$ -amylase and  $\beta$ -amylase are present in the milk of mothers delivering preterm infants. Levels of  $\alpha$ -amylase are similar in mothers delivering infants at 25 to 30 weeks, 31 to 35 weeks, and 36 to 40 weeks of gestation. Levels are highest in colostrum and then decline with increasing duration of lactation. (38)

Salivary  $\alpha$ -amylase levels are variable in preterm infants. Enzyme levels tend to be higher with increasing gestational age, but can be detected in preterm infants as young as 26 weeks’ gestation (the youngest age studied by the investigators). (39)

However, pancreatic  $\alpha$ -amylase levels are typically low in preterm infants. In one study, pancreatic  $\alpha$ -amylase was undetectable at birth, and remained so after 30 days of



feeding. (40) However, other studies have noted different findings. In neonatal piglets (an excellent model for human nutrition), pancreatic amylase is low in preterm compared with term piglets, but did increase after the start of enteral feedings (but not if the piglet was parenterally nourished). (41) It has been suggested that salivary  $\alpha$ -amylase may be able to partially compensate for low levels of pancreatic  $\alpha$ -amylase levels in preterm infants. (42)

The products of  $\alpha$ -amylase need to be converted to monosaccharides before absorption. This appears to be likely as the levels of sucrase, maltase, and isomaltase are usually comparable to the term infant. (43)

In practice, glucose polymers seem to be well absorbed in preterm infants. Absorption of glucose polymers has been assessed directly in infants (gestational age 28–42 weeks) using a gastrointestinal perfusion model. (44) This absorption increased with postnatal age, and with length of time on full enteral feedings. (44) In fact, absorption of glucose polymers was greater than that of lactose or of a combination of lactose and glucose polymers. (44)

### Monosaccharide Transport

The final steps of carbohydrate absorption in preterm infants is transport of glucose and galactose across the apical membrane of the enterocyte (via SGLT1) and then across the basolateral membrane into the circulation (via GLUT5). (45) Glucose transport across the gut appears to be intact in the fetal lamb (32 weeks' equivalent gestation) because intra-amniotic infusion of glucose leads to a rapid increase in fetal blood glucose, while no such increase is found for maltose or sucrose infusion. (25)

In a postnatal rat model, increased dietary carbohydrate increases glucose and galactose transport, as does increased enteral feeding. (45) Starvation and prolonged parenteral nutrition reduce glucose transport and it seems that "*luminal nutrition may be required to maintain glucose transporters.*" (45) Similar results are seen in preterm infants, with glucose absorption increasing as the proportion of milk feedings increases, and as feedings are infused over shorter periods. (46)

## FAT AND LIPID ABSORPTION

### Lipid Digestion and Absorption

Dietary lipids are important not only as a critical source of energy, but also as a substrate for bioactive compounds such as essential fatty acids, structural components of cell membrane, and regulators of gene expression.

### Fat Digestion in Adults

In adults, fat digestion begins in the mouth with lingual lipase that is secreted from the serous glands, and continues in the stomach with gastric lipase that is secreted by the chief cells in the fundus. Both enzymes have a preference for fatty acids on the sn-3 position of the triacylglycerol. Together they account for 10% to 30% of fat hydrolysis.

Chyme entering the duodenum stimulates the release of pancreatic lipases and colipase, which act synergistically in the digestion of emulsified fat. Pancreatic triglyceride lipase (PTL) seems to account for the majority of lipase activity in vitro. It binds to the oil/water interface of the triglyceride oil droplet, and preferentially hydrolyzes the triglyceride at the sn-1 and sn-3 positions. Many constituents of duodenal contents inhibit PTL, but colipase restores its activity by forming a complex that anchors PTL to the substrate. Phospholipase A catalyzes the hydrolysis of the fatty acid ester linkage at carbon 2 of phosphatidylcholine, leading to release of free fatty acid and lysophosphatidylcholine.

BSDL, also known as *carboxyl ester lipase*, has activity against various lipid substrates, but no human studies have suggested a function for BSDL in adults.

Bile, a mixture of mainly bile salts, phospholipids, cholesterol, and bicarbonate, is secreted by the liver and temporarily stored in the gallbladder. It is highly surface active, and acts as an emulsifier to ensure a large accessible surface area for the lipases. The absorption of many lipid-soluble substances, including cholesterol, vitamin D, vitamin K, and carotene, are almost completely dependent on the presence of bile. The products of triacylglycerol digestion, along with the bile salts, phospholipids, cholesterol, and other fat-soluble substances, form micelles in the small intestine.

### Fat Absorption in Adults

Despite its complexity, lipid digestion is very efficient and adults absorbed about 95% of dietary fat, regardless of fat intakes. Fatty acids with 12 or more carbon atoms are absorbed into the lymphatic system as chylomicrons, while those with 10 or fewer carbon atoms (short- and medium-chain fatty acids) are absorbed directly into the portal circulation.

Up to 50% of fat can be absorbed in the absence of bile, as free fatty acids, predominantly through direct portal absorption.

### Lipid Nutrition in Neonates

At birth, the human fetus switches from a predominantly glucose energy supply to a lipid-dominating source. Milk



fat provides 40% to 60% of the energy requirement in neonates. The content and composition of human milk fat varies with the mother's diet and stage of lactation. Human milk total lipid content increases during lactation from 2 g/dL in colostrum to 4.9 g/dL in mature milk. The ratio of saturated to unsaturated fat in human milk is similar to that in adipose tissue, and is appropriate for cell membrane function. Human milk fat is secreted as milk fat globules, which consist of a hydrophobic triacylglycerol-rich core enveloped by a triple layer membrane. This membrane contains amphipathic compounds such as phospholipids, proteins including enzymes, and cholesterol. It also contains membrane proteins and glycoproteins, and is rich in bioactive components.

The LCPUFAs, arachidonic acid and docosahexaenoic acid, are important functional components in human milk. These LCPUFAs are necessary for normal brain development as well as for immune function.

### Lipid Digestion in Neonates

Lipase accumulates in the proximal pouch of infants with esophageal atresia, consistent with a lingual site of production. (47) It is active at low pH and in the absence of bile salts.

Gastric lipase can be found in samples from fetuses as early as 18 weeks of gestation, attains significant levels of activity by 27 weeks, and reaches normal adult levels after the first few months of age. (48) Lipolytic activity is present in gastric aspirates as early as 26 weeks of gestational age in human infants. (47)

Predoduodenal (lingual and gastric) lipases are essential for the digestion of human milk fat because, contrary to pancreatic lipases, they can penetrate into the milk fat globule and initiate the digestive process. (49)

Even though some authors proposed that higher rates of gastric lipase activity may exist to compensate for the low pancreatic lipase activity, the pre- and postprandial gastric lipase concentration in infants is similar (50) or lower (51) than that in adults, and gastric lipolysis in premature infants is similar to that found in adults. (50)

Neonates have a relative exocrine pancreatic insufficiency, despite their high dietary fat intake. The capacity to digest fat is suboptimal at birth due to low pancreatic enzyme levels and low intraluminal bile salt concentrations. At birth, the expression of PTL and phospholipase A2 is very low or undetectable (52) and only reaches adult activity levels in the duodenum by 1 to 2 years of age. (53)

The 2 pancreatic enzymes predominantly involved in fat digestion early in life are BSDL and pancreatic lipase-related

protein 2 (PLRP2). PLRP2 messenger RNA is present by 16 weeks in the pancreas of human fetuses. (54) PLRP2 seems to have a minor digestive role, if any, in adults, but seems to play a significant role in the digestion of long-chain triglycerides when in the presence of colipase in infants. (55) Furthermore, in an in vitro model of human lipases and digestion of human milk and formula, PLRP2 has been shown to act synergistically with gastric lipase and BSDL from human milk in the digestion of human milk, especially in the presence of colipase. Predigestion with gastric lipase increased the activity of both enzymes in formula by 11-fold. (56)

BSSL, an enzyme with close similarity to the pancreatic BSDL, is present in human milk at all stages of lactation, even in mothers who deliver prematurely. (57) BSSL is inactive in the milk, but is activated by bile in the small intestine. BSSL has an optimal pH between 7.0 and 8.0 and requires bile salts for its lipolytic activity. Based on in vitro studies, BSSL activity is sufficient to completely hydrolyze milk triglycerides within 30 minutes in the small intestine. (58) However, BSSL is inactivated by heat (eg, pasteurization), (59) resulting in decreased fat absorption. (60)

Early in life, the reabsorption of bile salts is confined to the distal ileus and enterohepatic recycling is inefficient. In rats, active bile salt-transporting capacity increases with age, which may be related to a change in microvillus membrane lipid composition with increase in cholesterol resulting in a decrease in membrane fluidity. To what extent dietary effects contribute to these changes remains to be elucidated. (61) The postnatal development of the enterohepatic circulation results in an increase in the bile salt pool that leads to efficient absorption, as lipolysis and solubilization are better facilitated. Breastfed infants show a larger bile salt pool and higher intraluminal bile salt concentration than formula-fed infants, both at 11 and 35 days of age. (62)

Lipid absorption is lower in newborns than in adults. Term infants excrete approximately 10% of consumed lipids, whereas preterm infants excrete 10% to 30%. (63) The amount of unabsorbed fat appears to depend on gestational and postnatal age and the type of fat. (64) The absorption of saturated and long-chain fatty acids may be particularly impaired in formula-fed infants, especially for docosahexaenoic acid. (65)

Unabsorbed lipids reach the colon where they may be used by the colonic microbiota. However, the presence of prebiotic oligosaccharides may mask the effect of unabsorbed long-chain fatty acids on the colonic microbiome.

## PROTEIN, AMINO ACID, AND POLYPEPTIDE ABSORPTION

### Protein Digestion in Adults

Protein digestion is complex and involves a wide variety of enzymes. It occurs in 4 phases: gastric, luminal, mucosal/brush border, and intracellular.

**Gastric Phase.** Gastrin chief cells secrete 2 proenzymes, pepsinogen I and II, which are cleaved in the acid pH of the stomach into pepsin. Pepsin functions best at low pH and cleaves internal bonds, especially those involving phenylalanine, tyrosine, and leucine. Pepsin produces polypeptides and smaller oligopeptides. (66)

**Luminal Phase.** The pancreas secretes 5 main proteases; 3 are endoproteases (trypsin, chymotrypsin, and elastase) that cleave internal amino bonds, and 2 are exopeptidases (carboxypeptidase A and B) that cleave the terminal amino acid from the peptide, releasing a free amino acid. All are secreted as inactive zymogens. The most important is trypsin because it can activate all 5 zymogens to release the active protease. Trypsin itself is released from trypsinogen by brush border enterokinase or by trypsin (autolysis).

The different enzymes have different specificities for the various amino-amino bonds of proteins, and in concert, produce a mixture of oligopeptides, dipeptides, tripeptides, and free amino acids. (66)

**Mucosal/Brush Border Phase.** The brush border membrane contains a range of exopeptidases (including aminopeptidase N, aminopeptidase A, dipeptidylcarboxypeptidase, and dipeptidylaminopeptidase IV), endopeptidases, and dipeptidases to further digest peptides.

Di- and tripeptides can be transported into the cell by peptide transporter 1 while free amino acids are taken up by various amino acid transporters of different specificities. (67)(68)

**Intracellular Phase.** Intracellular proteases further digest the absorbed di- and tripeptides to free amino acids, which are transported into the basolateral cell membrane into the circulation using the same amino acid transporters found in the brush border. (66)

Most protein digestion and absorption occurs in the duodenum and jejunum. (66) But amino acid transporters are expressed in the colon and it is theoretically possible that unabsorbed amino acids might also be absorbed in the colon. (69) The functional contribution of amino acid transporters in the colon is unclear.

### Protein Digestion in Neonates

**Proteases in Human Milk.** A wide variety of proteases are present in human milk including anionic trypsin, anionic

elastase, plasmin, and both tissue-type and urokinase-type plasminogen activators cathepsin D and kallikrein. (70)

Most milk protease and antiprotease concentrations do not change with gestational age or postnatal age. However, this is not true of all human milk proteases. The concentration and activity of kallikrein, the most abundant and active protease in preterm milk, increases over time in milk from mothers of very premature infants, but remains more stable in the milk of mothers who deliver during mid- and late gestational age. (70)(71)

The action of carboxypeptidase B2 is higher in preterm milk than in term milk, and may explain the higher level of  $\alpha$ -1-casein-derived peptides found in preterm human milk compared with term human milk. (71) Plasmin activity is also higher, and endogenous human milk peptides are more abundant in preterm human milk than term human milk, especially in early lactation. (71) The higher protein degradation by endogenous proteases in preterm milk may contribute to improved net digestion in the immature digestive system of the premature infant. (71)

**Protein Degradation in the Stomach.** Pepsin is present in the stomach of fetuses as early as 16 weeks of gestation (72) and is produced at birth by both term and preterm infants, though at levels far lower than that of adults. (73) Recent studies on the peptidome in human milk suggest the presence of an enzyme with pepsinlike activity that may be seen at higher pH than pepsin. (74) Whether this is a novel enzyme not yet described in human milk remains to be elucidated.

Gastric aspirates of newborn infants also contain a protease with electrophoretic mobility and immunoreactivity similar to that of calf chymosin, a protease that cleaves  $\kappa$ -casein. This protease is unique in that it disappears from gastric fluid in the postpartum period and is not found in adult gastric fluid. (75)

Gastric proteolysis depends on the proteases present as well as the gastric pH, because pH influences enzyme activity. Typically, highly acidic pH causes protein denaturation, rendering the molecule more susceptible to protease cleavage. Because of their low acid production and the milk's buffering capacity, newborns maintain their postprandial gastric contents at near neutral pH, preventing protein denaturing. (76) Premature infants have a gastric pH of 5 to 7 for up to 1 hour after feeding, decreasing 3 hours after a feeding to a pH of 3 to 3.5. (50) The only human milk proteases with the potential to hydrolyze milk proteins at that pH are cathepsin D and plasmin. (77) These proteases seem to contribute very little to gastric protein digestion.

**Duodenal Protein Digestion.** Proteins present in human milk, human milk fortifiers, preterm formulas, and whey

protein concentrates are digested in vitro by duodenal juice from healthy preterm infants. (78) Casein is degraded most rapidly, and whey proteins more slowly. (78) Bovine whey proteins in human milk fortifiers and in preterm formulas are relatively slowly digested in vitro by normal duodenal juice. (78)

**Luminal Proteases.** Key luminal proteases involved in adult intestinal proteolysis (trypsin, chymotrypsin, elastase, enterokinase, and carboxypeptidase B) are present in both term and premature infants, but their concentrations and activities are much lower than those in adults. (79)

Enterokinase (which is responsible for activation of trypsin) has been detected in the duodenal mucosa of infants at 24 to 26 weeks of gestation (80) and it is present and active at birth in both term and premature infants. However, enterokinase activity was only 6% and 20% of that of older children in premature infants and term infants, respectively, (80) and trypsin concentration in the duodenum of premature infants is lower than in term infants. (81) At birth, both groups had lower trypsin activities than did adults, (40) but reached normal levels by 1 month of age. (40)(53)

Chymotrypsin and carboxypeptidase B are present in similar concentration and activity in duodenal fluids of both term and preterm infants at birth and at 30 days of age but lower than those found in older children and adults. (53)

In summary, even though major luminal proteases are present at birth and have similar activity in premature and term infants, particularly by 30 days after birth, lower enterokinase activity in the first several weeks may limit protein digestion in premature infants. (79)

**Brush Border Peptidases.** Once peptide fragments reach the brush border of the intestinal lining, a large variety of brush border peptidases such as di- and tripeptidases continue their breakdown. (82) Substantial quantities of brush border proteases, including  $\gamma$ -glutamyltranspeptidase, oligoaminopeptidase, dipeptidylaminopeptidase IV and carboxypeptidase, are present by 22 weeks of gestation, and some as early as 10 weeks of gestation. (82) Some enzymes have concentrations similar to those seen in older children and adults. The role of brush border peptidases early in fetal life is unclear but may contribute to extraction of amino acids from swallowed amniotic fluid, known to provide about 15% of fetal protein accretion. (83)

**Bacterial Proteases.** The bacteria of the intestinal microbiota also produce proteases and contribute to the digestion of dietary proteins. The resulting amino acids seem to be

metabolized rapidly by the bacteria. Various human intestinal bacteria can break down protein, including *Bacteroides* species, *Propionibacterium* species, and some members of *Streptococcus*, *Clostridium*, *Bacillus*, and *Staphylococcus*. (84) These proteins are first broken into peptides and then into volatile fatty acids, ammonia, dicarboxylic acids, and various phenolic compounds. (85) A wide variety of anaerobes can ferment amino acids.

## GASTROINTESTINAL MOTILITY

In addition to having the appropriate digestive and absorption machinery, preterm infants have other requirements to be able to successfully tolerate enteral nutrition including an adequate absorptive surface area and adequate gastrointestinal motility. Unless nutrients are able to pass from the stomach to more distal areas in the small intestine where they are absorbed, feeding will be unsuccessful. Anecdotally, most clinicians are able to recall very preterm infants (especially those of gestational age <24 weeks) whose feeding advancements were delayed by large gastric residuals (if they were being assessed), frequent emesis, or infrequent stools and abdominal distention.

The topic of gastrointestinal motility has been reviewed previously and will not be repeated in depth here. (86) Briefly, the intestinal motor pattern of the adult undergoes 5 phases after enteral feedings are given. This is known as the interdigestive migrating motor complex (IMMC).

Phase I: The motor activity of the gut is suppressed and little motor activity occurs.

Phase II: Single or multiple contractions develop at various levels of the gut, with limited coordination, and limited propagation along the gastrointestinal tract.

Phase III: Sustained contractions lasting up to 10 minutes develop and are propagated down the gastrointestinal tract in a coordinated manner.

Phase IV: Contractions once again become more random, and then quiescent.

During feedings, there are widespread uncoordinated contractions of the gut intended to mix the ingested food with digestive secretions and enzymes. (86)

The development of the IMMC is controlled by the cells of Cajal, stimulated in part by motilin. The cells of Cajal are typically present by 20 to 22 weeks' gestation and preterm infants can show evidence of gastrointestinal motility as early as 24 weeks' gestation, but a mature pattern of IMMC is rarely seen before 34 to 36 weeks. (86) The proportion of infants with a mature IMMC gradually increases with

gestational age, but up to 10% of term infants fail to show a mature IMMC at birth. (86)

Motilin levels in preterm infants are similar to those seen in adults, but they fail to cycle in the way those of adults do. (86) This may, in part, be responsible for the delayed onset of mature IMMC in preterm infants. Enteral feedings have been shown to increase the rate of maturity of gastrointestinal motor function, (86) which is another reason why enteral feedings should be encouraged.

Many of the anatomic requirements for gastrointestinal motor activity are present before 20 weeks of gestation, including the circular and longitudinal muscle layers, the myenteric plexus, the submucosal plexus, and mature neuroblasts.

## SUMMARY AND CONCLUSIONS

Macronutrient absorption by the preterm infant is generally good, though fat absorption is less than that seen in the adult. Many digestive enzymes and transport systems are present in the preterm infant or can be induced by exposure to substrates.

Exocrine pancreatic function is generally poor in preterm infants. Levels of pancreatic  $\alpha$ -amylase and pancreatic lipase, for example, are low in preterm infants. However, secondary mechanisms largely compensate for this deficiency.

The preterm infant has several important additional absorptive resources. The first source is the wide range of digestive enzymes present in human milk that may counterbalance poor pancreatic function. Examples include BSSL (lipid digestion) and proteases (protein digestion). The second source is the microbiome of the colon (including *Bifidobacterium*) that may assist in digestion of nutrients. The best example of this is the fermentation of HMOs into short-chain fatty acids, but it is also possible that colonic bacteria have a role in protein, amino acid, and fat digestion and absorption as well. Finally, the preterm infant may also have digestive enzymes that are not present in the adult (eg, BSSL, PLRP2, novel gastric proteases).

The preterm infant seems well-suited to continuing enteral feedings after birth, and the literature provides no reason for preferring parenteral over enteral feedings, and many reasons for preferring enteral feedings.

Difficulties with establishing enteral feedings are far more likely due to delayed gut motility rather than problems with nutrient digestion and absorption. Therefore, the primary route of nutrition for preterm infants should be the enteral route, unless clearly contraindicated.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the physiology of protein/amino acid digestion (absorption and metabolism) in newborn infants.
- Know the physiology of fat digestion, absorption, and metabolism in newborn infants.
- Know the physiology of carbohydrate digestion, absorption, and metabolism in newborn infants.
- Know the advantages and disadvantages of the use of donor human milk.

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# Index of Suspicion in the Nursery

## 1 Oral Burns as a Presentation of Accidental Organophosphorus Poisoning in a Neonate

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### PRESENTATION

A 5-day-old girl is brought to the hospital emergency department for excessive crying. There is a history of accidental oral administration of a liquid insect repellent by her 3.5-year-old sibling ~2 hours earlier. The bottle brought by the parents reads “mosquito repellent.” Examination reveals an irritable, excessively crying baby, possibly due to pain. Her vital signs are essentially normal, with a temperature of 99.7°F (37.6°C), a heart rate of 146 beats/min, a respiratory rate of 52 breaths/min, a prompt capillary refill time, blood pressure of 90/56 mm Hg, and saturation of 100% in room air. Her pupils are of normal size and responding normally. Her oral cavity shows extensive burns involving the palate and posterior pharyngeal wall with bleaching of the mucosa (Fig). There are no dermal burns. Systemic examination findings are normal. Investigations show normal blood sugar levels and serum biochemistry results. Findings on chest radiography are normal. The active ingredient is confirmed by a forensic laboratory at All India Medical Institute of Medical Sciences, New Delhi, as dichlorvos (organophosphorus [OP] compound) with a pH of 3 to 5.

After admission, the baby's eyes are cleaned with distilled water and her body is sponged dry to eliminate further risk of absorption. The baby receives supportive treatment, is kept nil orally, and is administered intravenous fluids. Antibiotics are started, and the baby is monitored for cardiovascular instability. Orogastric feeds are started after 4 days of admission. The baby is monitored and watched to exclude systemic infections. Direct breastfeeding could be started by 2 weeks, when most of the oral lesions are healed. The baby is discharged and is doing well on follow-up at 3 months.

### DISCUSSION

**AUTHOR DISCLOSURE** Drs Verma, Maria, and Singh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

OP compounds are commonly used as herbicides or insecticides in agriculture and households because they are relatively cheap and easily available. (1) Easy availability over the counter coupled with unsupervised use has led to an increase in the number of accidental and suicidal poisonings. Thus, neonates are rarely affected in such cases. Reported incidents among neonates have been



**Figure.** Extensive burns in the oral cavity of the patient caused by mosquito repellent.

the cases wherein the mode of exposure is transplacental, inhalation, or ingestion (accidental or homicidal). (2)(3)(4)(5)(6)(7)(8)(9) OP acts by inhibiting the enzyme cholinesterase in the central and peripheral nervous systems. The accumulated acetylcholine at synapses leads to cholinergic toxicity manifesting as miosis, bronchorrhea, excessive salivation, bradycardia, irregular respiration, and hyperpyrexia. (10) The local symptoms due to OP and features such as oral burns have not yet been reported to our knowledge. This case report presents an unusual case of oral burns in a neonate associated with accidental instillation of a domestic insecticide into the oral cavity by an older toddler sibling of the neonate.

Unlike in adults, where the poisoning is due to suicidal attempts, in infants it results from either unintentional accidental exposure or homicidal attempt. (2)(3)(4)(5)(6)(7)(8)(9) When affected, neonates are easily susceptible because of their large surface area. The signs and symptoms masquerade as neonatal sepsis. (5)(6)(7) Atropine being an antidote necessitates its differentiation for treatment. Typical muscarinic and nicotinic effects of OP poisoning are different in infants than in adults. Seizures, miosis, lacrimation, muscle weakness, dyspnea, and coma are common in infants. However, bradycardia, arrhythmia, hypotension, pulmonary edema, fasciculation, sweating, confusion, parkinsonism, psychosis, etc, are common in adults. (5)

Poisonings are difficult to identify in neonates because they require a high index of suspicion and exploration into preceding events as such incidents are not expected at this age. The diagnosis is based on history of exposure supported by the characteristic cholinergic signs. History of exposure may not always be evident. Presenting symptoms depend on dose, duration, route of

administration, and potency of the compound. The absorption of OP compounds could be through the gastrointestinal tract, skin, mucosal membranes (inhalational and through the conjunctiva), and, rarely, transplacental. The Table shows a brief review of the literature on cases of neonatal OP poisoning along with the management and outcome.

Oral burns are common manifestations of caustic and acid ingestion, caused by denaturation of surface proteins. The stronger the acid ( $\text{pH} < 2$ ) or alkali ( $\text{pH} > 11$ ), the higher its potency to cause burns. Acids cause extensive coagulative necrosis of proteins, whereas alkalies cause liquefactive necrosis of mucosa. Mucosal burns involving the oral cavity, esophagus, and stomach may culminate in stricture formation. The OP compounds rarely produce oral burns, and neonates may be more susceptible to the tissue-damaging effects of OP compounds because their mucosa is more fragile. However, it seems that this type of presentation probably reflects the milder end of the spectrum of presentation of OP poisoning. This infant had no systemic manifestations in the acute phase and recovered fully, with no sequelae on follow-up.

Unknown poisoning presenting with oral burns can be misdiagnosed if muscarinic or nicotinic symptoms are not present, as is the case with OP poisoning in neonates and children. In the presence of a specific antidote, a missed diagnosis can be fatal. The diagnostic hallmark of OP poisoning is reduction in serum and red blood cell cholinesterase activity. Although most cases of neonatal OP poisoning in the literature have been treated with atropine and pralidoxime (Table), we managed the case conservatively due to the absence of systemic symptoms. There was no dysphagia or feed intolerance in this infant. Because the infant was accepting feeds well and the lesions healed gradually, an endoscopy was deferred. In our case, with child abuse ruled out, the circumstantial evidence was overwhelming in favor of accidental OP poisoning, as confirmed by laboratory testing. The literature review does not have any record of a case of oral burns caused by OP compounds.

An OP compound poisoning warrants a differential diagnosis for the etiology of oral burns in neonates. Decisions should be made in the wake of clinical examination such that an absence of systemic toxicity should not be misleading.

### Lessons for the Clinician

Little is reported about OP poisonings in neonates. This report may inform the treating physician with newer insights on this subject, especially the following:

- Neonatal age is not exempt from OP poisoning.

TABLE. Neonatal OP Poisoning: Literature Review

SOURCE	AGE, d	MODE OF POISONING	SIGNS AND SYMPTOMS	SERUM ACETYL CHOLINESTERASE LEVELS	TREATMENT GIVEN	OUTCOME
Sarkar et al, (2) 1994	1	Transplacental: propoxur	Copious secretions, miosis, flaccid paralysis, twitching	Not determined	Atropine, pralidoxime, supportive treatment	Death due to perinatal asphyxia and carbamate poisoning Duration of stay 4 d
Kaur et al, (3) 1996	25	Not known	Increased secretions, bradycardia, pinpoint pupils, hypotonia, irregular respiration	2.14 nmol product formed/min per mg protein	Atropine, pralidoxime, supportive treatment	Discharged healthy Duration of stay 20 d
Jajoo et al, (4) 2010	1	Transplacental: Diazinon	Shallow respiration, bradycardia, poor perfusion, profuse secretions, dilated pupils, twitching	Not determined	Atropine, pralidoxime, supportive treatment	Discharged healthy Duration of stay 12 d
O'Reilly and Heikens, (5) 2011	12	Compound not known: probable accidental topical exposure	Increased oral secretions, poor feeding, diarrhea, pinpoint pupils, hypotonia, pulmonary edema	Not determined	Atropine, supportive treatment	Discharged healthy Duration of stay 5 d
Parvez et al, (6) 2012	17	Diazinon spray: accidental topical absorption/ inhalation	Poor feeding, reduced activity, increased oral secretions, apnea, bradycardia, pinpoint pupils	137 U/L	Atropine, pralidoxime, supportive treatment, stopping breastfeeding	Discharged healthy on day 2, readmission, and again discharged
Chheda et al, (7) 2014	15	Homicidal ingestion: Thimet (10% phorate)	Excessive secretions from mouth, poor feeding, irregular respiration, nystagmus, pinpoint pupils	Initial: 466 U Repeated on day 2: 566 U	Atropine, pralidoxime, supportive treatment	Death due to multi-organ failure Duration of stay 4 d
Meena and Kumar, (8) 2014	6	Oral accidental exposure, compound not known	Poor oral acceptance, lethargic, jitteriness, increased nasopharyngeal secretions, hypotonia, pinpoint pupils	0.25 kU/L	Atropine, pralidoxime	Discharged healthy Duration of stay 6 d
Kumar et al, (9) 2015	8	Oral accidental ingestion of chlorpyrifos	Inconsolable cry, poor feeding, seizures, bradycardia, respiratory distress, pinpoint pupils, copious secretions	2,209 IU/L	Atropine, pralidoxime	Discharged healthy Duration of stay 18 d

- However, presentation may be unusual, such as oral burns.
- In the presence of circumstantial suggestion, OP poisoning must be considered, even if systemic cholinergic signs are absent.

#### ACKNOWLEDGMENT

We acknowledge Dr. A. Jaiswal, Scientist Poisoning Cell, All India Institute of Medical Sciences, New Delhi, for identifying the OP compound in our case.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the complications and management of various neonatal skin injuries, including intravenous infiltrates and chemical and thermal burns.

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## Case 1: Oral Burns as a Presentation of Accidental Organophosphorus Poisoning in a Neonate

Ankit Verma, Arti Maria and Archana Singh

*NeoReviews* 2019;20:e37

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# Index of Suspicion in the Nursery

## 2 Asymmetrical Frontal Bossing and Refractory Seizures in a Newborn

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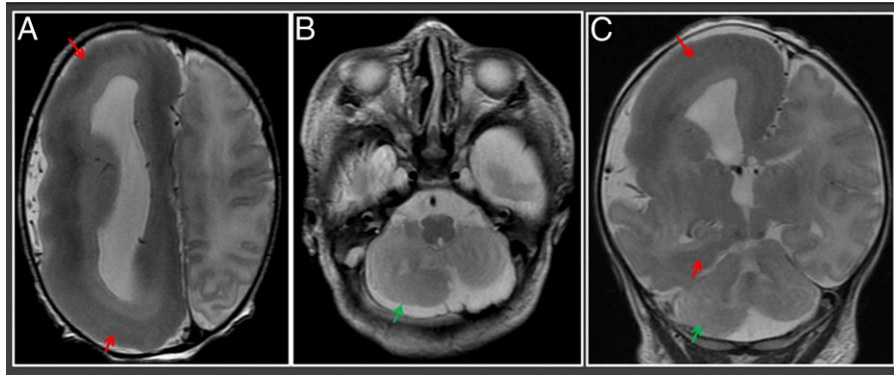
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### PRESENTATION

A male infant is born at 37 6/7 weeks' gestation by repeat cesarean delivery to a 33-year-old gravida 2, para 0 mother who had a previous fetal demise at 37 weeks' gestation (etiology unknown; no autopsy performed). For this current pregnancy the mother had regular prenatal care. Gestational diabetes was treated with dietary interventions. The mother is deaf due to childhood meningitis. She has a history of genital herpes simplex virus (HSV), with no active lesions at the time of delivery while receiving suppressive valacyclovir. The delivery is complicated by a nuchal cord and difficult extraction. The infant requires brief positive pressure ventilation. Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, are given. The infant weighs 3,735 g and is noted to have macrocephaly, with a head circumference of 15.8 in (40 cm). His length is 19.7 in (50 cm) and plots at 52%. He has a large open anterior fontanelle and asymmetrical frontal bossing, with prominence of the right forehead. The remainder of his newborn examination findings are normal. At 2 hours after birth he develops intermittent oxygen desaturations associated with arching of his back followed by right-sided shaking. His blood sugar level is 78 mg/dL (4.3 mmol/L). He is placed on 1-L nasal cannula oxygen and is loaded with 20 mg/kg of phenobarbital for suspected seizures. A blood culture is performed, and he is started on ampicillin, gentamicin, and acyclovir. A normal saline fluid bolus is given, and maintenance fluids are initiated at 80 mL/kg per day. The infant is then transferred to a facility that provides a higher level of care.

On arrival at our facility he is noted to be hypotonic and requires nasal cannula oxygen at 2 L. The results of his complete blood cell count and comprehensive metabolic panel are normal; rapid plasma reagin test is nonreactive; and surface HSV, urine, and blood cultures are negative. Lumbar puncture showed 9 white blood cells/ $\mu$ L ( $\times 10^9$ /L), 10 red blood cells  $\times 10^6$ / $\mu$ L ( $\times 10^{12}$ /L), a protein level of 0.15 g/dL (1.5 g/L), a glucose level of 56 mg/dL (3.1 mmol/L), and Gram-stain/culture negative. Results of cerebrospinal fluid HSV polymerase chain reaction are negative. Computed tomographic scan shows right hemisphere hypertrophy that extends past midline, with hydrocephalus on the right and an unformed left lateral ventricle. Initial video electroencephalography the day after birth was abnormal, with tracé alternant pattern and sharp transients in all 4 quadrants, both excessive for age. There was no evidence of seizure activity.

**AUTHOR DISCLOSURE** Drs Frey, Hogden, and Berg have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



**Figure.** Axial (A) and coronal (C) T2-weighted magnetic resonance images demonstrate overgrowth of the right cerebral hemisphere with an enlarged, misshapen right lateral ventricle. There is absent sulcation in the right frontal and parietal lobes and reduced sulcation in the right temporal lobe. The cortex is markedly thickened (red arrows) in the right frontal and parietal lobes, as well as in the right medial temporal lobe. Axial T2 weighted image (B) demonstrates asymmetrically enlarged right cerebellar hemisphere (green arrow), also visualized in (C).

Further imaging includes a brain magnetic resonance image (MRI) (Fig) that reveals a diffusely abnormal right cerebral hemisphere, which is asymmetrically enlarged, with an enlarged, misshapen lateral ventricle consistent with hemimegalencephaly (HME). There is almost complete absence of sulcation involving the right frontal and right parietal lobes. There are rudimentary sulci present in the right temporal and right occipital lobes. The cortex is diffusely abnormal in appearance and thickened, with probable bandlike regions of gray matter heterotopia. Callosal dysgenesis is noted. There is asymmetry in the size of the cerebellar hemispheres, with the right being slightly larger than the left. The folia in the right cerebellar hemisphere also appear abnormal in the areas with thickening of the gray matter cortex.

By day 3 after birth the infant is off supplemental oxygen, is taking feeds orally, and has completed a 48-hour antibiotic/antiviral course after cultures were noted to be negative. That evening he develops abnormal eye movements and arm twitching, prompting an electroencephalography that demonstrates continuous high-voltage theta waves (~250–300 msec duration) in the right hemisphere that quickly generalized. The seizure continued for ~26 minutes, with a return to right hemispheric rhythmic activity for most of this time. After the initial prolonged seizure there was a period of ~4 hours without seizures, following which seizures recurred with a frequency consistent with status epilepticus, almost entirely in the right hemisphere. After the administration of multiple medication boluses (fosphenytoin, levetiracetam, lorazepam, midazolam, and phenobarbital), the frequency of seizures decreased and there was a period of ~9 hours with only a few brief seizures. Most of the seizures were without recognizable clinical changes.

However, the infant's status epilepticus recurs and proves refractory to multiple antiepileptic medications.

He receives additional boluses of levetiracetam, fosphenytoin, and phenobarbital and eventually a continuous infusion of midazolam. He develops respiratory depression and requires mechanical ventilation.

Based on the MRI findings and a Pediatric Neurology consultation, the infant is diagnosed as having HME. Given the inability to adequately control his seizure activity, consultation is made with an institution able to perform hemispherectomy for seizure control of a patient with HME. While preparing for transfer the infant develops metabolic acidosis, shock, and disseminated intravascular coagulation. The transfer is canceled due to the patient's instability. On day 11 after birth, due to continued worsening of his condition, the decision is made to redirect care to comfort measures. The infant is extubated and dies within minutes. The parents consent to a limited autopsy to obtain a brain biopsy for genetic testing. A somatic overgrowth gene set panel was performed, with no pathogenic or likely pathogenic variants identified.

## DISCUSSION

### The Condition

Hemimegalencephaly is a rare congenital malformation of the brain characterized by abnormal proliferation of part or all of 1 cerebral hemisphere with resultant extreme asymmetry. (1)(2) It is classified as a malformation attributed to abnormal neuronal and glial proliferation where anomalies of neural proliferation represent the primary event and alterations of neural cell migration occur secondarily. (1) (2) It is a rare condition reported in 1 to 3 of 1,000 epileptic children, with a mild prevalence in boys. (1) There are 3 types of HME. The first type, isolated HME, is the most common type, manifesting the typical brain findings but without

any cutaneous or systemic involvement. The second type, systemic HME, is associated with partial or total hemigigantism and/or certain neurocutaneous syndromes, including epidermal nevus syndrome, Proteus syndrome, Klippel-Trenaunay-Weber syndrome, hypomelanosis of Ito, and neurofibromatosis type 1. The third type, and most infrequent, is total HME in which in addition to the affected cerebral hemisphere there is enlargement of the ipsilateral cerebellum and brain stem. (1)(3)

Clinically, asymmetrical macrocrania is the main physical finding and may be the only sign noted at birth. Evidence of increased intracranial pressure is usually absent due to progressive adaptation of the fetal skull to the abnormal brain growth. Hemigigantism and classic skin findings are noted with the systemic varieties of HME. The classic neurologic triad seen in all forms of HME includes psychomotor retardation, contralateral motor deficit, and epilepsy. Seizures occur in more than 90% of affected individuals and are usually severe, progressive, and medication resistant. (1) Seizures usually begin during the first days after birth and are heterogeneous, including motor partial seizures, tonic and atonic seizures, spasms, myoclonic jerks, and early epileptic encephalopathy. Early resistance to antiepileptic drug therapy is the main characteristic of epilepsy in HME. (1)(3) A correlation between an earlier onset of epilepsy and the degree of severity of the motor deficit and intellectual level has been reported. (4)

The pathogenesis of HME is incompletely understood. Recent genetic studies implicate a somatic mutation in the cells of the affected hemisphere during early cerebral development. (3)(5)(6)(7)(8) De novo somatic mutations involving the *PIK3CA*, *AKT3*, and *MTOR* genes, which encode regulators of mechanistic target of rapamycin (mTOR) signaling, have been identified. (4)(5)(6)(7)(8) mTOR is a protein kinase that directs a signaling network that senses and integrates environmental cues to regulate cell division, growth, and survival. (8)(9) Gain-of-function mutations upregulate the mTOR pathway, altering neuronal growth and metabolism signaling. (3)(4)(7)(8)

## Diagnosis

Fetal ultrasonography can raise suspicion for HME with identification of macrocephaly or ventricular asymmetry. However, MRI is the gold standard for diagnosis. (3) Almost all cases will demonstrate a malformed hemisphere with abnormal enlargement (mild to marked) and possible midline shift. The ipsilateral lateral ventricle is abnormal in size and shape. The cortical mantle is thick, with poor gray-white matter differentiation. The gyral architectural pattern

demonstrates areas of agyria, pachygyria, polymicrogyria, and lissencephaly that may alternate with areas of normal gyration. (1)(3)

## Treatment

Most affected individuals will require multiple antiepileptic medications to control seizure activity. Frequent, refractory, intractable seizures may respond favorably to hemispherectomy. (3)(10) The goal of surgery is the complete resection or disconnection of epileptogenic zones, leaving the patient with less seizure burden and minimal postoperative neurologic deficits. Seizure control can be achieved in approximately 50% to 60% of patients with hemispherectomy, although most children will have persistent neurologic sequelae. (1)(10)

Anatomical hemispherectomy is associated with the highest rate of postoperative seizure control. Bleeding complications are significant with this procedure. (1) Functional hemispherectomy with disruption of the connecting nerves and tissues while leaving the hemisphere in place is an alternative. (1)

Improvement of either the motor function level or intellectual development was seen in most patients after functional hemispherectomy in a survey of Japanese patients with HME. Early surgical intervention (reported in patients as young as 3 months) is recommended for the early-onset epilepsy group to preserve psychomotor development. (1)(4)

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the familial/genetic features of neurologic disorders associated with increased head circumference.
- Understand the differential diagnosis and evaluation of neonatal seizures.

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## Case 2: Asymmetrical Frontal Bossing and Refractory Seizures in a Newborn

Teresa Frey, Laurie Hogden and Aaron Berg

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# Index of Suspicion in the Nursery

## 3 Severe Anemia in a Term Newborn

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### PRESENTATION

A term 2,935-g appropriate for gestational age boy is born to a 22-year-old gravida 2, para 1001 woman at 38 and 1/7 weeks' gestation via an induced vaginal delivery. She received regular prenatal care and is followed closely during her pregnancy for maternal isoimmunization. The mother's laboratory tests reveal a blood type of AB, Rh negative, human immunodeficiency virus types I and II nonreactive, hepatitis B antigen nonreactive, rapid plasma reagin negative, and rubella immune. Her antibody screen is positive for warm autoantibodies to G and C with a combined titer of 1:64. Prenatal ultrasonography at 20 weeks notes a left atrophic multicystic kidney, a normal right kidney, and no other congenital anomalies. The mother is monitored with serial ultrasonography, revealing a stable, normal-range middle cerebral artery Doppler until 32 weeks' gestation. Her 32-week ultrasonography demonstrates a middle cerebral artery of 1.9 multiples of median. Amniocentesis yields a bilirubin level of 0.022 OD 450 nm, corresponding to zone 1 on the Liley curve, indicating mild or no disease. At 38 and 1/7 weeks the mother is noted to have a nonreactive nonstress test. Delivery is induced, and she proceeds to have an uncomplicated vaginal delivery.

After delivery, delayed cord clamping is performed for 45 seconds. The infant has a weak cry, but with adequate respiratory effort. A saturation probe is placed, revealing oxygen saturation of 52%. A 3/6 holosystolic murmur, mild to moderate retractions, and pallor are noted on examination. He is given blow-by oxygen at 100% fraction of inspired oxygen, which increases his oxygen saturation to 80%. The infant remains pale throughout the resuscitation and is transferred to the NICU.

### PROGRESSION

A complete blood cell count is notable for a hematocrit value of 19%, normal red blood cell indices, and normal peripheral smear. Other laboratory values include a total bilirubin level of 2.8 mg/dL (47.88  $\mu$ mol/L), an absolute reticulocyte count percentage of 1.3%, direct antibody test positive, and antibody screen positive for C antibody. Results of a maternal Kleihauer-Betke test are negative. The infant is started on fluids and given 5 mL/kg packed red blood cell transfusion over 4 hours. His hospital stay includes 2 days of phototherapy for an elevated bilirubin level. He is confirmed to have a left atrophic multicystic kidney on postnatal ultrasonography and is referred to nephrology for follow-up. An echocardiogram shows a moderate atrial

**AUTHOR DISCLOSURE** Ms Do and Drs Motz and Parikh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

septal defect and a large patent ductus arteriosus, so cardiology follow-up is arranged. A thorough physical examination before discharge notes no syndromic features. His hematocrit value on discharge is noted to be 30%.

On follow-up in the hematology clinic at 10 days after birth he is noted to have a hematocrit level of 25% and is given a 10-mL/kg blood transfusion. At 2 months of age he is admitted for respiratory distress and pallor. At that time his hematocrit value was noted to be 5.3%. Further evaluation with a bone marrow biopsy reveals the diagnosis.

## DISCUSSION

### Diagnosis

On bone marrow biopsy, the patient was noted to have erythroid hypoplasia, with follow-up genetic studies revealing a pathogenic mutation at S ribosomal protein 24. A diagnosis of Diamond-Blackfan anemia (DBA) was made.

The differential diagnosis for neonatal anemia is broad but can be divided into blood loss, increased destruction, and decreased production. (1) The initial diagnosis for our patient's anemia seemed to be an obvious case of isoimmunization. The low reticulocyte count was puzzling, but in broadening the differential diagnosis we noted that our patient did not yet meet the diagnostic criteria for DBA. Nonetheless, we arranged follow-up with hematology for monitoring and further evaluation.

Diamond-Blackfan anemia is a congenital condition of bone marrow failure characterized by impaired erythropoiesis due to familial (autosomal dominant) or sporadic mutations affecting ribosome synthesis. (2) It is a rare disease with an annual incidence of 5 to 7 cases per million live births. Affected patients classically present within the first year after birth with a severe macrocytic anemia and reticulocytopenia that is often associated with congenital anomalies. Characteristic facial features have been reported; however, a wide range of congenital anomalies, such as ophthalmologic, cardiac, neck, thumb, and genitourinary, can also occur. (3)(4) An association with malignancy has also been suggested previously. (5)

Subsequent bone marrow biopsy reveals normal cellularity with paucity of erythroid precursors, and further genetic analysis reveals a characteristic mutation in S ribosomal proteins that causes failure of erythropoiesis. The

classic diagnosis of DBA is made when certain criteria are met: age younger than 1 year, isolated macrocytic anemia, reticulocytopenia, and normal marrow cellularity with paucity of erythroid precursors. A probable diagnosis is made if the previous criteria are not met but the patient has an associated gene mutation, a positive family history, or a combination of other minor laboratory anomalies. (1)(3)(4)(6)

Neonatal anemia due to decreased red blood cell production includes transient erythroblastopenia of childhood (TEC), Fanconi anemia, Schwachman-Diamond syndrome, and dyskeratosis. The latter 3 diagnoses are characterized as aplastic anemias that present with pancytopenia and hypocellular bone marrow, which help differentiate them from DBA. (2)(7)

TEC is a transient acquired condition of decreased red blood cell production of currently unknown etiology. Patients often have a preceding viral illness and a more moderate form of anemia. Other distinguishing features of TEC include presentation after a year of age, a normocytic anemia, and no congenital anomalies. (2)(8) These characteristics are distinct from DBA and aid in making the correct diagnosis. (9)

### Treatment and Prognosis

Mainstays of treatment include corticosteroids and blood transfusions; hematopoietic stem cell transplant is an option for patients with corticosteroid-refractory disease. (5)

The body of research regarding the rare diagnosis of DBA continues to grow, with a focus on expanding the treatment options and elucidating the incidence of associated malignancy via the DBA Registry. (6)

### Lessons for the Clinician

- The differential diagnosis for neonatal anemia is broad but can be divided into blood loss, increased destruction, and decreased production.
- Neonatal anemia can be due to multiple concurrent causes.
- Specialist follow-up for neonatal conditions is a necessary and critical component of an appropriate NICU discharge.
- Diamond-Blackfan anemia is a congenital condition of bone marrow failure characterized by impaired erythropoiesis due to familial (autosomal dominant) or sporadic mutations affecting ribosome synthesis.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology and pathophysiology of hemolytic anemia in the neonate.
- Know the clinical and laboratory features of hemolytic anemia in the neonate.
- Know the causes of and diagnostic approach to an infant who is anemic at birth.
- Know the clinical indications for use of blood products in neonates, as well as the manifestations and prevention of potential complications of transfusion.

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### Case 3: Severe Anemia in a Term Newborn

Julie Do, Patrick Motz and Pratik Parikh

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**Case 3: Severe Anemia in a Term Newborn**

Julie Do, Patrick Motz and Pratik Parikh

*NeoReviews* 2019;20:e45

DOI: 10.1542/neo.20-1-e45

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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## Recurrent Late Decelerations in a Patient with HELLP Syndrome

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

**AUTHOR DISCLOSURE** Drs Meram, Pederson, and Ouyang have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

#### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

- Bradycardia not accompanied by absent variability
- Tachycardia
- Minimal or marked baseline variability
- Absent variability without recurrent decelerations
- Absence of induced accelerations after fetal stimulation
- Recurrent variable decelerations with minimal or moderate variability
- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

- Absent variability with any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## PRESENTATION

### History

A 33-year-old gravida 1, para 0 pregnant woman with a history of chronic hypertension presented at 37 2/7 weeks' gestation for a routine prenatal visit and was noted to have new 1+ proteinuria. Her antenatal course and medical history were notable for type A2 gestational diabetes mellitus, obstructive sleep apnea, hypothyroidism, pseudotumor cerebri, and class III obesity (body mass index=50.4 kg/m<sup>2</sup>). Her most recent ultrasonography scan at 31 weeks' gestation showed an estimated fetal weight of 1,926 g (51st percentile). During her prenatal appointment, the patient reported feeling well, and denied having any headaches, visual disturbances, right upper quadrant pain, or other symptoms of preeclampsia. Her blood pressure was 134/72 mm Hg. She had a reactive nonstress test and normal amniotic fluid volume assessment. In light of her proteinuria, a laboratory evaluation was performed to assess for preeclampsia; the results were significant for a platelet count of  $103 \times 10^3/\mu\text{L}$  ( $103 \times 10^9/\text{L}$ ), aspartate aminotransferase (AST) of 53 U/L ( $0.89 \mu\text{kat/L}$ ), alanine aminotransferase (ALT) of 143 U/L ( $2.39 \mu\text{kat/L}$ ), and an elevated protein-creatinine ratio of 0.57. Induction of labor was recommended because of suspected onset of hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome.

### Case Progression

On arrival at the labor and delivery department, the patient's initial blood pressure was 162/90 mm Hg. Her cervical examination showed that she was 1 cm dilated, 20% effaced, and at -3 station. The FHR is shown in Fig 1.

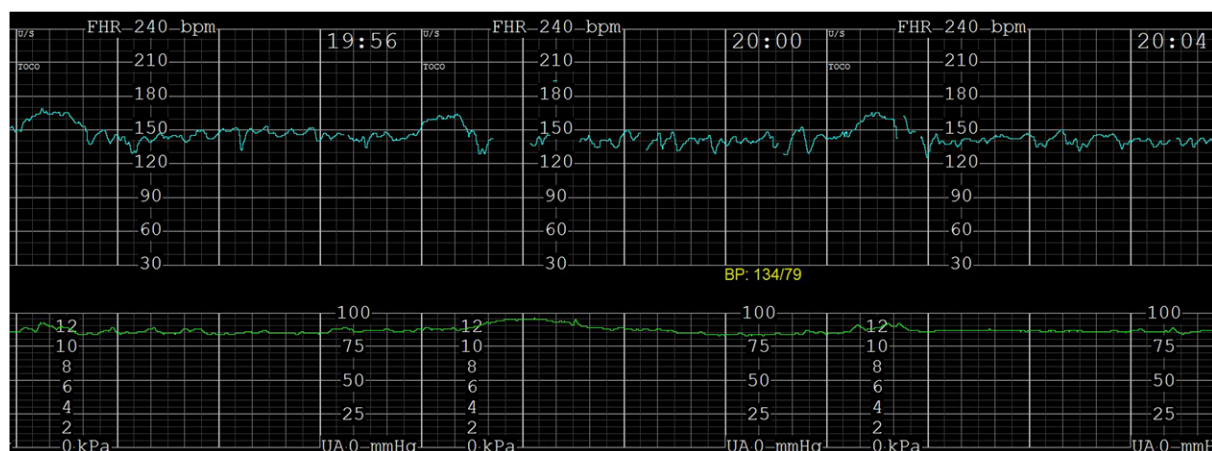


Figure 1. Electronic fetal monitoring strip 1.

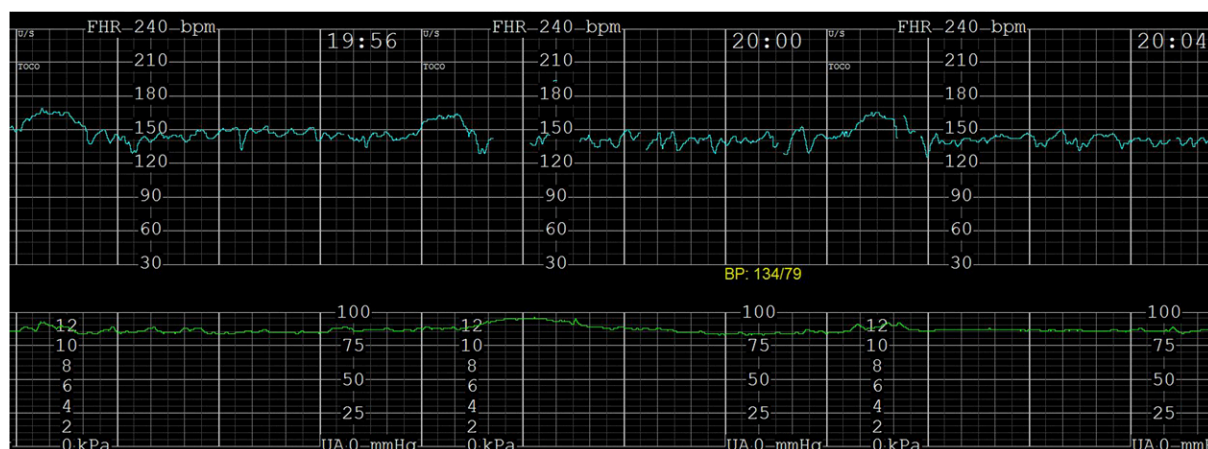


Figure 1. Electronic fetal monitoring strip 1.

Findings in Fig 1:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: Every 5 to 10 minutes lasting 30 to 60 seconds
- Interpretation: Category I
- Differential diagnosis: Reassuring FHR tracing
- Action: Proceed with induction of labor

Due to unfavorable cervical examination findings, induction was initiated with mechanical ripening with a Foley balloon and concurrent oxytocin. Magnesium sulfate was

initiated for seizure prophylaxis. Laboratory tests for pre-eclampsia were repeated and notable for a decreasing platelet count to  $89 \times 10^3/\mu\text{L}$  ( $89 \times 10^9/\text{L}$ ) and increasing liver enzymes with AST and ALT of 61 U/L ( $1.02 \mu\text{kat/L}$ ) and 146 U/L ( $2.4 \mu\text{kat/L}$ ), respectively. Because of her worsening thrombocytopenia and discomfort with contractions, an epidural catheter was placed. Her cervical Foley balloon catheter was removed after 12 hours, with her cervix 2 cm dilated, 75% effaced, and at -3 station. She underwent artificial rupture of membranes and an intrauterine pressure catheter was placed because of difficulty obtaining a continuous tracing due to maternal obese habitus. She continued to progress appropriately to 4.5 cm dilation, 75% effacement, and -3 station. The FHR is shown in Fig 2.

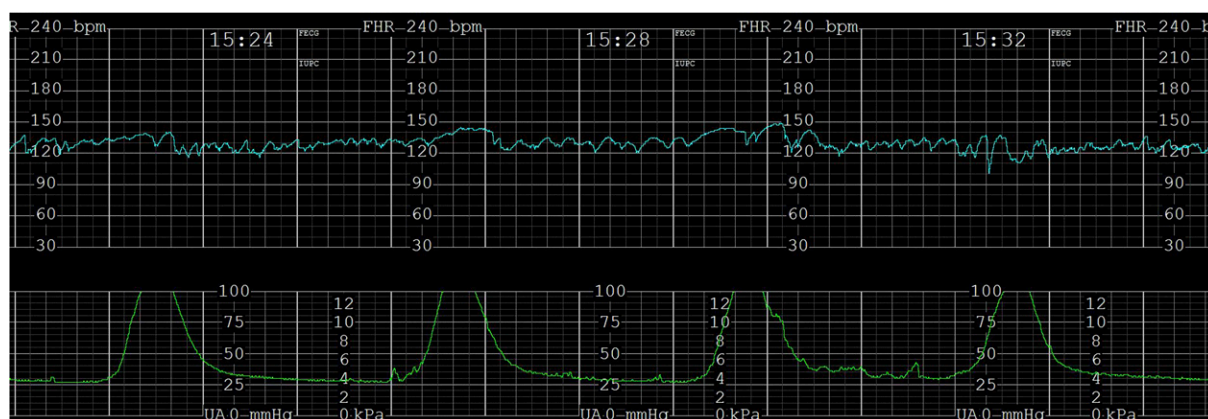


Figure 2. Electronic fetal monitoring strip 2.

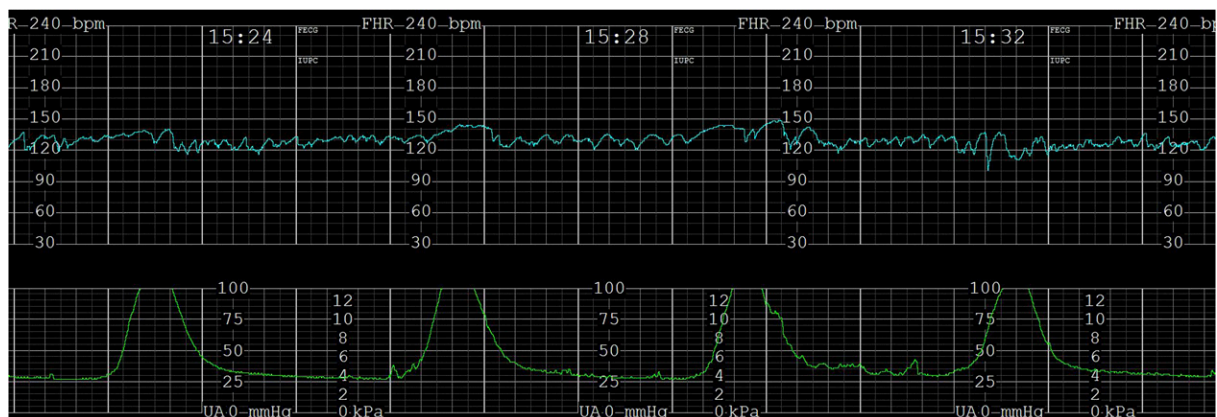


Figure 2. Electronic fetal monitoring strip 2.

Findings in Fig 2:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Interpretation: Category I
- Differential diagnosis: Reassuring FHR tracing

- Action: Continue with induction of labor
- Uterine contractions: Every 3 minutes lasting 60 seconds

Approximately 24 hours after initiating the induction, the patient began experiencing increased pain that was not adequately relieved by the epidural. An epidural bolus was given. Shortly afterward, the patient became hypotensive with a blood pressure of 70/50 mm Hg. The FHR is shown in Fig 3.

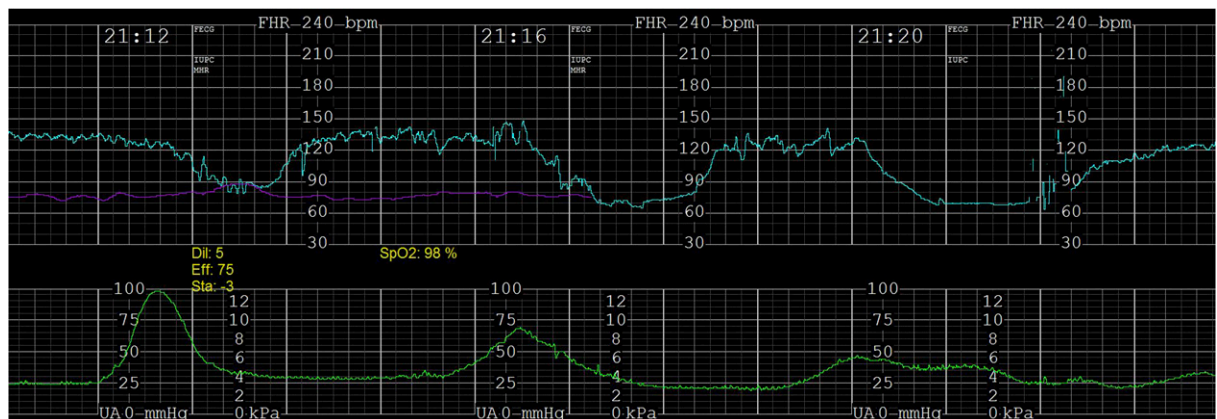


Figure 3. Electronic fetal monitoring strip 3.



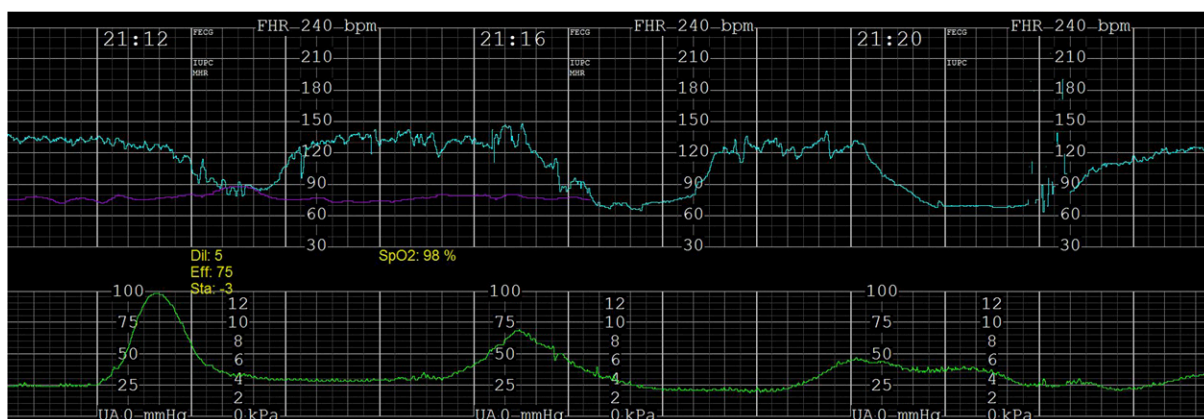


Figure 3. Electronic fetal monitoring strip 3.

Findings in Fig 3:

- Variability: Moderate
- Baseline rate: 130 beats/min
- Episodic patterns: None
- Periodic patterns: Recurrent late decelerations
- Uterine contractions: Every 2 to 4 minutes lasting 60 to 90 seconds
- Interpretation: Category II

- Differential diagnosis: Uteroplacental insufficiency due to hypotension, placental abruption
- Action: Resuscitative measures

### Outcome

The patient was placed in the left lateral decubitus position, supplemental oxygen was administered, and oxytocin was stopped. She received an intravenous fluid bolus as well as ephedrine 5 mg intravenously. Her blood pressure improved to 107/64 mm Hg. The FHR tracing is shown in Fig 4.

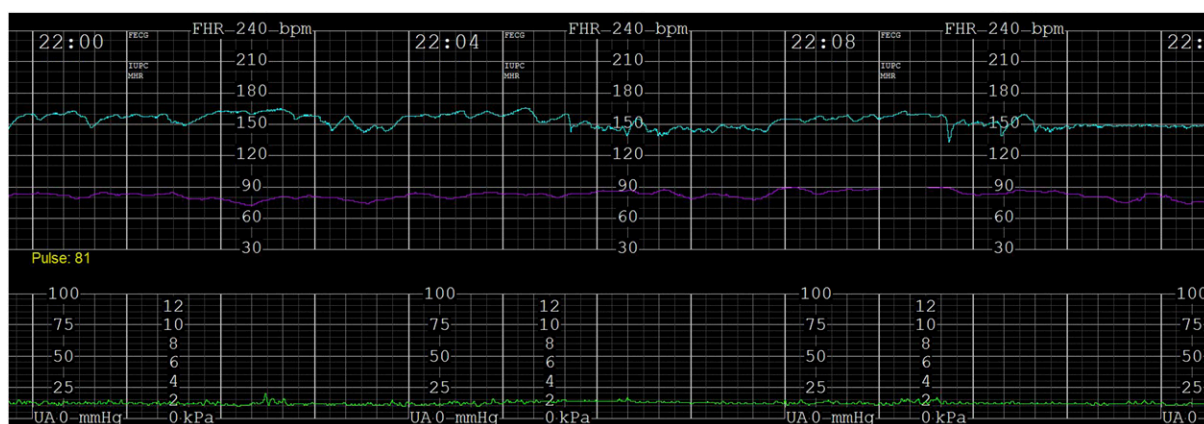


Figure 4. Electronic fetal monitoring strip 4.

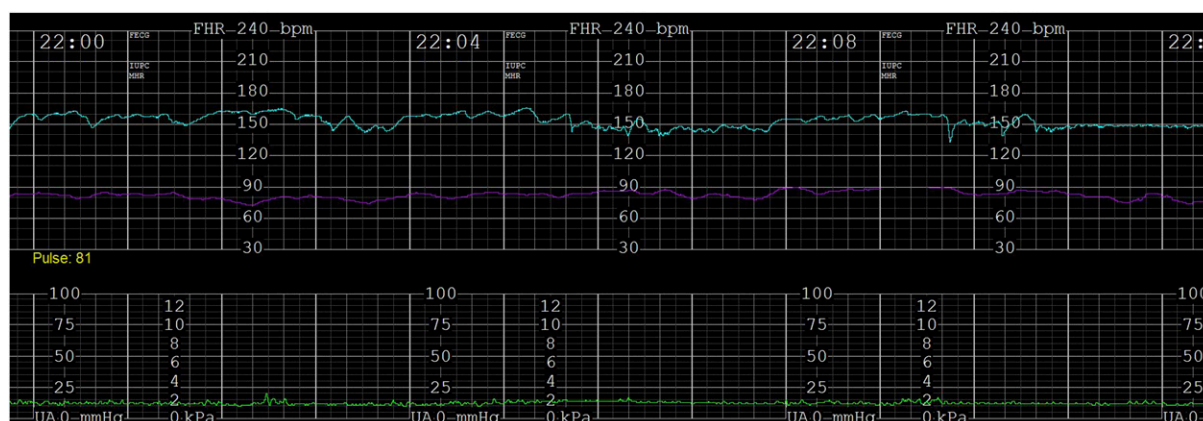


Figure 4. Electronic fetal monitoring strip 4.

Findings in Fig 4:

- Variability: Moderate
- Baseline rate: 150 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: Not detectable
- Interpretation: Category I
- Differential diagnosis: Reassuring FHR tracing
- Action: Continue induction of labor

After approximately 30 minutes of a category I tracing, oxytocin was restarted. She continued to progress in labor and had a spontaneous vaginal delivery of a male infant weighing 2,695 g approximately 33 hours after initiating the induction of labor. The Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Quantitative blood loss was 650 mL. Cord gases were as follows: arterial pH 7.23, venous pH 7.29 with a base excess of  $-6.0$ . The infant had an uncomplicated hospital course and was discharged from the hospital on day 2 after birth.

## DISCUSSION

Epidural anesthesia and analgesia are neuraxial anesthetic techniques that involve inserting a catheter through a needle placed between 2 adjacent vertebrae, and injecting anesthetic medications into the epidural space via the catheter. The epidural space is bordered anteriorly by the dura and posteriorly by the ligamentum flavum. During labor, after placement of the epidural catheter and an initial bolus, anesthetic medications are typically infused continuously into this space through the catheter until delivery of the infant and the placenta and complete repair of any perineal lacerations.

Epidural analgesia during labor is usually achieved with a combination of a local anesthetic, such as dilute ropivacaine

or bupivacaine, and an opioid, such as fentanyl. The addition of an opioid to the local anesthetic acts synergistically to decrease the dose and concentration of local anesthetic required and increase the onset of anesthesia. (1)

While the benefit of labor epidural analgesia is to provide substantial and site-specific pain relief for laboring patients, similar to any medical procedure, an epidural can also have adverse effects, including maternal hypotension. This complication occurs in approximately 10% of patients who receive an epidural, which is lower than the rate of hypotension with spinal anesthesia. The reasons for this include the slower rate of onset and decreased density of the neural blockade with epidural. (2)

Epidural analgesia-mediated hypotension is primarily the result of local anesthetic-induced sympathetic blockade. This sympathectomy leads to dilation of the venous capacitance vessels below the level of the block and a subsequent decrease in venous return to the heart (ie, decreased preload). Decreased preload then leads to a lower stroke volume and cardiac output, resulting in systemic hypotension. (3) Additional factors contributing to hypotension in this setting include decreased maternal catecholamines after the relief of labor pain following the epidural bolus and the intravascular volume contraction associated with pre-eclampsia/HELLP syndrome.

During labor, maternal hypotension can cause significant and critical changes in the FHR tracing. Profound and abrupt onset of maternal hypotension can result in decreased uteroplacental perfusion, which if not corrected, can lead to fetal hypoxia. On the FHR tracing, this can manifest as bradycardia and recurrent and/or prolonged decelerations with a corresponding increased risk in urgent cesarean delivery. (4)

Several strategies are used to reduce the possibility of epidural-induced hypotension. These include the

administration of a bolus of intravenous crystalloids either before or during epidural placement, and positioning the pregnant woman into a lateral position after epidural placement to avoid compression of the vena cava. (5) Because of the slower onset of epidural-induced hypotension compared with that of spinal anesthesia, vasopressors are not routinely administered prophylactically before epidural placement.

Treatment of epidural analgesia-related hypotension centers around restoring preload and sympathetic tone by rapidly infusing boluses of intravenous fluids and administration of vasopressors. (6) Ephedrine, a mixed  $\alpha$  and  $\beta$  agonist, is an appropriate and commonly used first-line agent in doses of 5 to 10 mg intravenously. Pure  $\alpha$  agonists, including phenylephrine and norepinephrine, can also be considered, and are more commonly used to treat hypotension following spinal anesthesia for cesarean delivery.

In general, a nonreassuring FHR tracing due to hypotension will resolve with correction of the hypotension. In the current case, the patient became hypotensive shortly after receiving a bolus of epidural anesthesia. She then received an infusion of intravenous fluids as well as ephedrine. As her hypotension resolved and uterine blood flow increased, the FHR improved to a category I tracing that resulted in a healthy neonate.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effects on the fetus and/or newborn infant of maternal surgery and anesthesia (eg appendectomy).

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## Strip of the Month: Recurrent Late Decelerations in a Patient with HELLP Syndrome

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## Neonate with a Large Facial Swelling

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### CASE

A full-term male newborn presents with a large hemifacial swelling extending from the frontal region to the mandibular region, encroaching on the orbit and displacing the pinna. (Figs 1 and 2)



Figure 1. Large hemifacial swelling on the right side of the face displacing the pinna.

### Prenatal and Birth Histories

- Born to a 36-year-old gravida 3 para 2 woman at 40 weeks' gestation after elective cesarean delivery
- Previous 2 siblings were both healthy
- No family history of similar lesions
- No history of trauma in this pregnancy
- Maternal prenatal screening was negative
- Level 2 antenatal ultrasonography was performed at 20 weeks' gestation, and results were normal; results of follow-up fetal growth scans were normal
- Antenatal ultrasonography had been performed 1 day before delivery and showed a homogenous hyperechoic space-occupying lesion involving the right side of the face extending up to the temporal area, measuring 6 × 4 cm
- Infant cried immediately after birth and did not need any resuscitation

**AUTHOR DISCLOSURE** Drs Gupta, Garg, Thakur, Agrawal, and Kler have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





Figure 2. Swelling encroaching on the orbit.

### Presentation

At birth, the infant was noted to have a hemifacial swelling over the right temporal area. Investigations showed persistent thrombocytopenia, and the lowest platelet count was  $51 \times 10^3/\mu\text{L}$  ( $51 \times 10^9/\text{L}$ ). No platelet transfusion was required before transfer. The infant was referred 9 days after birth to our institution for further management.

### PROGRESSION

#### Vital Signs (Day 9)

- Heart rate: 140 beats/min
- Respiratory rate: 50 breaths/min
- Blood pressure: 60/40 mm Hg (mean, 47 mm Hg)
- Oxygen saturation: 95% (in room air)
- Temperature: 98.5°F (36.9°C)

#### Physical Examination (Day 9)

- Birthweight = 2,800 g (fourth percentile), length = 50 cm (30th percentile), head circumference = 36.5 cm (85th percentile), weight at admission = 2,985 g (third percentile)
- Skin: No icterus,  $9 \times 5$  cm, nontender facial swelling on the right side of the face encroaching on the orbit and displacing the pinna, with discoloration of overlying skin

- Eyes (fundus): Normal
- Head: Normocephalic; normal, open, flat fontanelles; symmetrical facies; patent nares; intact palate; no neck mass or crepitus
- Oral cavity: Pink mucosae, intact palate, no lymphadenopathy, normal sucking and rooting reflex
- Lungs: Clear, equal breath sounds; no respiratory distress
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallop
- Abdomen: Not distended; no organomegaly
- Genitourinary: Normal term male genitalia; patent anus
- Skeletal: Spine appears normal
- Neurologic: Consolable, symmetrical Moro reflex, normal strength and tone

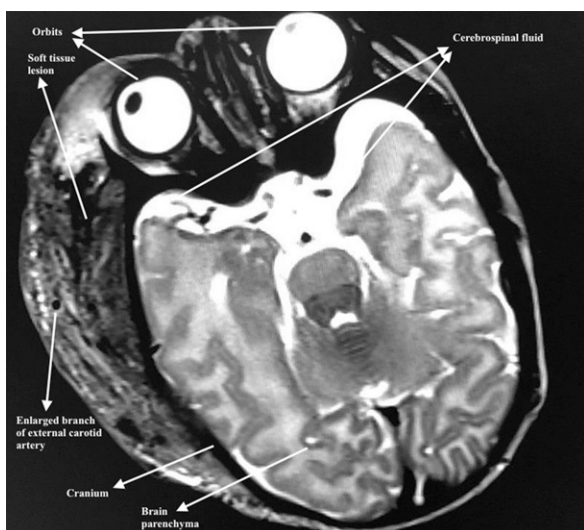
#### Laboratory Studies (Day 9)

- White blood cell count:  $13,000/\mu\text{L}$  ( $13 \times 10^9/\text{L}$ ), with 31% neutrophils and 51% lymphocytes
- Immature/total neutrophil ratio: 0.18 (reference range in term infants,  $<0.2$ )
- Hemoglobin level: 11.9 g/dL (11.9 g/L)
- Platelet count:  $16 \times 10^3/\mu\text{L}$  ( $16 \times 10^9/\text{L}$ )
- Activated partial thromboplastin time of 54 seconds (mean  $\pm$  SD reference range,  $42.6 \pm 8.62$  seconds), prothrombin time of 16 seconds (mean  $\pm$  SD reference range,  $12.4 \pm 1.46$  seconds), international normalized ratio of 1.44 (reference range,  $<1.5$ )
- D-Dimer levels: 13.7  $\mu\text{g/mL}$  (75.0 nmol/L) (reference range,  $<0.2 \mu\text{g/mL}$  [ $<1.1$  nmol/L])
- C-reactive protein level: 0.4 mg/L (3.8 nmol/L) (reference range,  $<10$  mg/L [ $<95.2$  nmol/L])
- Urinalysis: Normal
- Blood and urine cultures: Negative
- Thyrotropin: 4.03 mIU/L (reference range,  $-1.7$  to 9.1 mIU/L)

#### Radiographic Studies

Magnetic resonance imaging of the brain and face was performed and showed a large infiltrative lesion with central areas of hemorrhage involving the right temporalis, pterygoid, and masseter muscles; the parotid gland; the anterior and posterior walls of the external auditory canal; and the retroauricular region with infiltration into the parapharyngeal and masseteric space without intracranial or intraorbital extension (Figs 3–5).

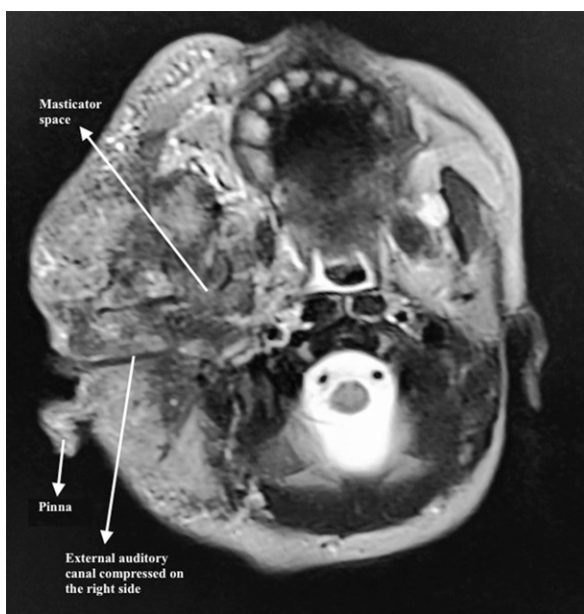
Doppler evaluation of the lesion showed a few high-flow (arterialized) segments. Abdominal ultrasonography showed a normal liver.



**Figure 3.** Magnetic resonance image (T2 weighted) at the level of the orbit showing involvement of the preseptal space on the right side, with no postseptal or intraconal extension seen.

## DIFFERENTIAL DIAGNOSIS

Kaposiform hemangioendothelioma  
 Kasabach-Meritt phenomenon associated with a hemangioma  
 Lymphatic malformation  
 Plexiform neurofibroma  
 Rapidly involuting congenital hemangioma  
 Rhabdomyosarcoma

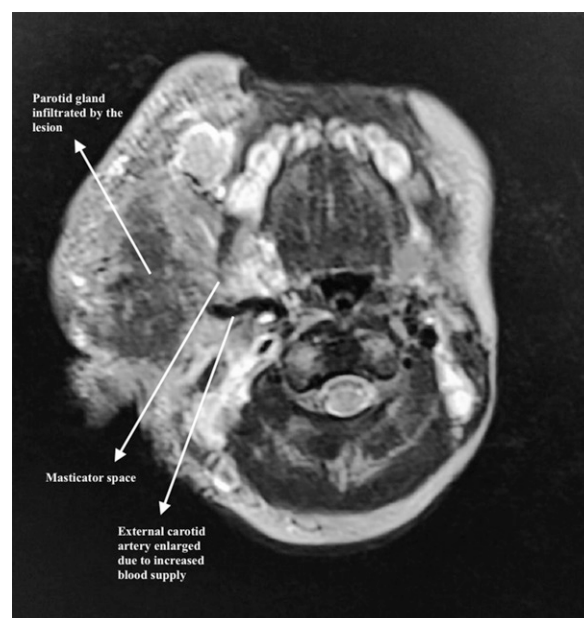


**Figure 4.** Magnetic resonance image (T2 weighted) showing a collapsed external auditory canal due to mass effect of the surrounding lesion.

## ACTUAL DIAGNOSIS

A large hemifacial hemangioma with persistent thrombocytopenia due to trapping of platelets and elevated D-dimer levels suggestive of consumptive coagulopathy was consistent with a diagnosis of Kasabach-Meritt phenomenon (KMP). A possibility of Kaposiform hemangioendothelioma was considered, but the classical feature of plaque-like lesions with ill-defined margins usually located on the extremities and trunk was not present. Abdominal ultrasonography ruled out hemangioma in the liver. Findings from echocardiography and a detailed eye examination were normal. A possibility of associated hypothyroidism was ruled out by a normal thyrotropin value.

Treatment with oral propranolol was initiated at 1 mg/kg per day on day 10 after birth; this was gradually increased to 3 mg/kg per day by day 15. The infant received multiple platelet transfusions for treatment of persistent thrombocytopenia. At 16 days of age, in view of poor clinical response, oral prednisolone was initiated at a dose of 2 mg/kg per day. Subsequently, vincristine at a dose of 1 mg/m<sup>2</sup> as a weekly injection and oral sirolimus 0.8 mg/m<sup>2</sup> twice a day were added sequentially to the treatment regimen in view of increasing size of the hemangioma and persistent severe thrombocytopenia. Serial complete blood cell counts during the hospital course are shown in the Table. The lesion was noted to be reducing in size from 4 weeks of age (Fig 6). Prednisolone was gradually tapered over 3 weeks; however,



**Figure 5.** Magnetic resonance image (T2 weighted) showing infiltration of the parotid gland by the lesion and enlargement of the external carotid artery.



**Figure 6.** Infant at 1 month of age with reduction in the size of the hemangioma.

propranolol was continued as a good response rate is reported if it is used for a longer duration. (1) With the reduction in size and improving trend of platelet count the infant was discharged at 5 weeks of age on oral propranolol, sirolimus, and weekly vincristine injections.

The infant was readmitted to the hospital 3 weeks after discharge with presenting complaints of fever and lethargy. Treatment with antibiotics was started after obtaining a complete blood cell count, C-reactive protein, blood, urine, and cerebrospinal fluid (CSF) cultures. His hemoglobin level was 7.6 g/dL (76 g/L), total leukocyte count was  $3,400/\mu\text{L}$  ( $3.4 \times 10^9/\text{L}$ ) (with a lowest absolute neutrophil count of  $810/\mu\text{L}$  [ $0.8 \times 10^9/\text{L}$ ]), and platelet count was  $24 \times 10^3/\mu\text{L}$  ( $24 \times 10^9/\text{L}$ ). His C-reactive protein level was 105.8 mg/L (1,007.6 nmol/L). Sirolimus therapy was

discontinued, and granulocyte colony-stimulating factor (filgrastim) was administered in view of febrile neutropenia. None of the culture specimens (blood, urine, and CSF) showed any growth. Antibiotics were discontinued after 10 days because the infant improved clinically and blood counts normalized. Thrombocytopenia resolved by 10 weeks of age.

The infant was also noted to have a hoarse cry and paucity of movement in all 4 limbs 48 hours after admission. A possibility of vincristine-induced neuropathy was considered. Results of nerve conduction velocity tests performed for motor nerves (upper limb: left median and left ulnar nerves; lower limb: left common peroneal and left posterior tibial nerves) and sensory nerves (upper limb: left median nerve; lower limb: left sural nerve) confirmed the diagnosis. Other evaluations for neuropathy included concentrations of creatine phosphokinase and vitamins D and B<sub>12</sub>; these were all normal. Treatment for neuropathy included discontinuation of vincristine, pyridostigmine (3 mg/kg orally every 12 hours), and pyridoxine (40 mg orally every 8 hours), along with physiotherapy. There was some improvement in upper limb movements, and the infant was discharged from the hospital at 11 weeks of age.

#### Follow-up

On follow-up at 4 months the infant was thriving and the size of the hemangioma was significantly reduced (Fig 7). The infant continues to receive oral propranolol, pyridostigmine, and pyridoxine. His upper limb movements have recovered almost completely, with significant improvement in his lower limbs as well.

#### What the Experts Say

Infantile hemangiomas are the most common vascular tumors of infancy. (2) Prevalence in neonates is 4.5%, with

**TABLE. Serial Complete Blood Cell Counts During the Disease Course**

	AT BIRTH	DAY 2 OF AGE	DAY 9 OF AGE	DAY 13 OF AGE	DAY 21 OF AGE	DAY 25 OF AGE	DAY 30 OF AGE
Total leukocyte count, $/\mu\text{L}$ ( $\times 10^9/\text{L}$ )	10,700 (10.7)	12,700 (12.7)	13,000 (13)	9,000 (9)	4,600 (4.6)	6,900 (6.9)	9,300 (9.3)
Hemoglobin, g/dL (g/L)	13.4 (134)	15.1 (151)	11.9 (119)	6.9 (69)	7.4 (74)	7.8 (78)	8.1 (81)
Platelet count, $\times 10^3/\mu\text{L}$ ( $\times 10^9/\text{L}$ )	100 (100)	51 (51)	16 (16)	6 (6)	7 (7)	7 (7)	37 (37)

We supported profound thrombocytopenia (platelet count  $<10 \times 10^3/\mu\text{L}$  [ $<10 \times 10^9/\text{L}$ ]) with platelet transfusion. Six units of platelets were given from day 9 to day 25 of age. Platelet transfusions at a higher threshold were avoided because these may be futile in Kasabach-Merritt phenomenon due to the known feature of possible platelet trapping.





Figure 7. Infant at 4 months of age.

a female predominance. (3) Associated antenatal risk factors include older maternal age (as in our case), preeclampsia, and other placental anomalies. (3) Infantile hemangiomas demonstrate a characteristic sequence of rapid growth followed by spontaneous regression. Large facial hemangiomas (>5 cm in size) can be associated with a syndrome described by the acronym *PHACES* (posterior fossa abnormalities, hemangioma, arterial anomalies, cardiac lesions, eye abnormalities, sternal cleft), and these should be ruled out by appropriate investigations. Another associated entity is KMP, which is a hemangioma associated with severe thrombocytopenia resulting from intralesional platelet trapping with elevated D-dimer levels, as in our case. (4) Prothrombin time and activated partial thromboplastin time are normal or marginally increased.

Diagnosis of infantile hemangioma is mainly clinical; magnetic resonance imaging may be helpful in ascertaining the extent of the lesion. The main indications of treatment include airway compromise (hemangiomas in the beard area with coexisting airway lesions), risks of functional impairment (covering the eye), obstruction, ulceration, and disfigurement (especially in the case of facial hemangiomas). Oral propranolol (2–3 mg/kg per day in 2 divided doses) has been described as the first line of treatment, with a response rate of 96% to 98% after 6 months of treatment. (1) The infant was closely monitored for adverse effects of propranolol, which commonly include hypoglycemia, hypotension, and bradycardia. (1) A topically administered  $\beta$ -blocker (timolol) is also effective in smaller, nonulcerated lesions. (5) It reduces blood flow through the hemangioma and minimizes the adverse effects of an oral agent. (6) Timolol 0.5% is applied topically to the lesion 3 to 5 times a day. (5) Systemic corticosteroids (2–3 mg/kg per day) are also used as first-line treatment but may be associated with

adverse effects such as increased risk of infection, osteoporosis, and adverse effects on growth. (7)

Second-line treatment includes vincristine, which inhibits cell mitosis and causes apoptosis of tumor and endothelial cells. It is administered as an intravenous injection at a dose of 1 to 1.5 mg/m<sup>2</sup> weekly. Its major adverse effect is mixed motor and sensory neuropathy (which progresses distally to proximally), autonomic neuropathy, and cranial neuropathy, which can manifest as vocal cord paresis (hoarse/weak voice). Neuropathy usually presents 2 to 19 weeks after commencing treatment. (8) Pyridostigmine (3–6 mg/kg per day) and pyridoxine (150–300 mg/m<sup>2</sup> per day) have neuroregenerative effects and have been used for treating vincristine-induced neuropathy. (9)(10) Sirolimus downregulates mammalian target of rapamycin implicated in vascular proliferation. It may be administered orally (0.8 mg/m<sup>2</sup> twice a day) in refractory cases. Adverse effects include mucositis and neutropenia.

Kaposiform hemangioendothelioma can also be complicated by KMP and presents as a plaque-like lesion with ecchymosis. Lymphatic malformations are not associated with thrombocytopenia and skin color changes. Plexiform neurofibromas are not seen at birth, present as lid hypertrophy or swelling, and are associated with café-au-lait patches. Rhabdomyosarcomas are the most common soft tissue sarcoma in children; however, age at onset is typically 2 to 5 years. Rapidly involuting congenital hemangiomas are fully grown at birth, characterized by superficial prominent veins encircled by a pale halo, and do not increase in size further.

To summarize, most infantile hemangiomas regress spontaneously. However, life-threatening hemangiomas, or those that can lead to KMP or functional impairment, need treatment, close monitoring, and follow-up.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know how to diagnose and manage Kasabach-Merritt syndrome.

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## Neonate with a Large Facial Swelling

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# Historical Perspectives

## Lessons from the BetterBirth Trial: A Practical Roadmap for Complex Intervention Studies

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### BACKGROUND

Complex interventions—those that contain several interacting components—to improve clinical outcomes and population health are growing because of the increasing recognition that multilevel approaches are needed to solve complex problems in health systems and care delivery. (1) In maternal and neonatal health, complex interventions are needed to improve quality of care. Yet few studies of these complex interventions are powered to detect true differences in mortality because of the numbers needed for a relatively rare outcome, such as maternal mortality. Although perinatal mortality is more common, large sample sizes are still required. Studies are often powered to examine outcomes or process measures proximal to mortality, such as morbidity or complications that could lead to mortality. The BetterBirth Trial was one of the largest cluster randomized controlled trials (RCTs) to target maternal and perinatal mortality as primary outcomes. Given its scale, this trial has led to important lessons learned that could be applied to other large-scale studies with complex interventions in maternal and newborn health.

Many epidemiology and biostatistics textbooks have described how to theoretically design RCTs to maximize scientific rigor. (2) However, there are few, if any, resources on how to actually implement complex interventions on a large scale, evaluate their impact, and disseminate the results. (3) Balancing an unbiased and robust study design with the reality of implementing a complex intervention in the real world can pose ongoing challenges for research teams. Some generally accepted best practices to minimize common challenges of trial implementation do exist, such as for institutional review board navigation, site selection, and stakeholder engagement. This perspective reflects on the experience of the BetterBirth Trial and provides insights around best practices of important components of trial design and implementation that may be initially overlooked.

**AUTHOR DISCLOSURE** Drs Molina and Semrau and Ms Bobay have disclosed funding from the Bill & Melinda Gates Foundation Grant OPP1017378: Better Birth: The WHO Safe Childbirth Checklist Trial. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

RCT     randomized controlled trial  
ToC     theory of change  
WHO     World Health Organization

### THE BETTERBIRTH TRIAL

The BetterBirth Trial was a matched-pair cluster RCT designed to establish whether the BetterBirth intervention was effective in reducing early (7-day)

maternal mortality and morbidity and perinatal mortality in Uttar Pradesh, India. (4) The BetterBirth intervention was developed to improve the quality of intrapartum care through the World Health Organization (WHO) Safe Childbirth Checklist (WHO Checklist) and accompanying implementation strategy focused on facility leadership buy-in, staff engagement, peer-to-peer coaching, and data feedback. The trial included a total of 120 primary-level facilities and enrolled approximately 160,000 woman-newborn pairs. While adherence to essential birth practices increased among birth attendants in intervention facilities, there was no impact on maternal mortality and morbidity or perinatal mortality. (5) Given the scale of this trial, we propose a roadmap of practical lessons learned to mitigate or plan for similar challenges in designing and implementing other studies around large-scale complex interventions: partnerships and collaboration, theory of change (ToC), formative work and pilot testing, intervention implementation strategy, data quality assurance systems, and dissemination strategy.

### Partnerships and Collaboration

A foundational principle of global health research is partnership with local experts through designing, testing, and communicating results. (6) To implement a trial of this size, scope, and scale, we established a collaboration among research, implementation, and government partners, which was essential to the success of the study. Ariadne Labs, a joint innovation center at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, led the research in collaboration with Community Empowerment Lab and Jawaharlal Nehru Medical College in India. The Governments of India and Uttar Pradesh collaborated on study design and implementation, leading the study's tripartite agreement for implementation. Key priorities in our collaboration were rigorous methodology, high-quality data collection and interpretation, and dissemination of results locally and globally through context-specific communications. WHO provided a global policy perspective and aided in development and early testing of the WHO Safe Childbirth Checklist, and Population Services International implemented the study in Uttar Pradesh. The trial funder, the Bill and Melinda Gates Foundation,

participated in decisions about study location and design, but did not provide input on data collection, management, analysis, or interpretation of the data. Their partnership was important for understanding the funding landscape and learning about other projects in Uttar Pradesh that may have influenced the BetterBirth Trial. In addition, we established a scientific advisory committee of researchers, clinicians, and public health professionals that provided oversight for the study and supported interpretation of the results.

### Recommendations.

- Clearly outline roles and responsibilities with established deliverables for optimal collaboration.
- Utilize multidisciplinary expertise because it is deeply valuable for complex interventions and results in stronger interventions and implementation approaches.
- Clarify roles around communication of the study, including peer-reviewed authorship, early in the collaboration and revisit as needed.
- Develop an advocacy plan with policy leaders and key stakeholders who are not part of the study team but who will be affected by the study results.
- Maintain open communication with funders about deliverables and budget limitations, including possible modifications to either based on learnings along the way.

### Theory of Change

A ToC is a “theory of how and why an initiative works, which can be empirically tested by measuring indicators for every expected step on the hypothesized causal pathway to impact.” (7) This is often represented as a visual map of the underlying hypothesis behind the research question for complex interventions and program evaluations. The BetterBirth Trial had a basic ToC: the BetterBirth intervention (WHO Checklist implemented through facility engagement, peer coaching, and data feedback) would lead to increased adherence with the 28 essential birth practices listed in the WHO Checklist, and this behavior change would lead to improved maternal and newborn outcomes (Fig). This ToC, however, was overly simplified and did not account for every expected step between the increased adherence to practices and decreased mortality and morbidity.



Figure. BetterBirth theory of change. Graphic image courtesy of Ariadne Labs.



### Recommendations.

- It is a valuable exercise to develop a comprehensive ToC for any complex intervention study or program evaluation.
- The ToC should be reviewed and refined with all relevant stakeholders, including the research/evaluation team and the implementation team.
- Map every primary and secondary outcome and their measurement to the ToC.
- Ensure that research and implementation teams understand the ToC.
- Use consistent language and develop a communication strategy around the ToC to drive the research and implementation forward, especially when multiple teams are involved and staff turnover occurs.
- Anticipate potential lessons learned if the hypothesis is proven true *and* if it is proven false. Develop the ToC so that it can help with interpretation of the study findings, regardless of whether they are positive or null.

### Formative Work and Pilot Testing

Nearly all complex intervention studies require a phase of formative work or background research to understand the relevant contextual factors for the study site(s). This phase may occur while developing the grant proposal and may continue through the beginning of the grant period. Subsequent pilot testing may take place depending on the stipulations of the grant. In preparation for the BetterBirth Trial, formative work was done with a diverse group of experts and stakeholders around developing the items on the WHO Checklist. (8)

Once the content of the WHO Checklist was established, a pilot pre-post intervention study was conducted in Karnataka, India, in 2010, which demonstrated improvement from an average of 10 of 29 essential birth practices to 25 of 29 after implementation of the WHO Checklist. (9) This pilot study provided promising results that supported the first part of the underlying ToC at a subdistrict-level hospital in Karnataka, India. However, the BetterBirth intervention needed to be adapted for primary-level facilities in Uttar Pradesh. The BetterBirth team revised the intervention through an adaptive design process with implementation, evaluation, and feedback in Uttar Pradesh. (10) An important lesson learned through this process was the importance of peer-to-peer coaching instead of physician-led coaching to support behavior change in birth attendants.

### Recommendations.

- Formative work around the context at study facilities is essential for understanding and defining the problem. Results from this work should then inform the design and implementation of any complex intervention,

especially those that depend on behavior change. Examples of topics that should be explored for intrapartum quality improvement interventions include birth attendant competency (knowledge, skills, and attitudes), women's preferences around childbirth and relevant societal norms that may influence health-seeking behavior, motivation and incentive structures in health facilities, leadership and management structures, referral systems, and workflow analysis regarding how the intervention would integrate into existing workflows.

- If possible, a pilot study should be conducted in a similar context to the one that will be used for the large-scale trial.
- Gathering qualitative and quantitative information during the pilot phase is critical because it is an opportunity to fail quickly and learn deeply. Observations, workflow mapping, interviews, and focus group discussions can provide insights into how the intervention functions in real-world circumstances beyond the information collected in quantitative surveys.
- Some complex interventions may require multiple adaptation cycles to ensure they are optimally integrated into the workflow and organizational culture of the facilities.
- While some adaptations may be required, it is important to consider that making too many changes at once may result in an inability to identify which change was most important.

### Intervention Implementation Strategy

Complex interventions developed for large-scale trials or evaluations require clear implementation strategies so that they are implemented in a standardized way. The BetterBirth team developed an implementation guide that outlined the distinct phases of intervention implementation: Engage, Launch, and Support. (11) First, the Engage phase included gaining commitment from facility, district, and state leadership for implementing the BetterBirth intervention. This phase also included adaptation of the WHO Checklist to Uttar Pradesh Ministry of Health guidelines. Second, the Launch phase included a motivational event to introduce the checklist to the birth attendants and assess existing quality gaps at the facility. We used locally produced videos and flipbooks to support the Launch event. (12)(13) Last, the Support strategy included a tapered 8-month peer-to-peer coaching program to encourage adoption of practices in the checklist and resolve barriers, and a data feedback structure through which coaches shared visual observation charts with facility and district staff to foster change. To facilitate sustainability, local facility champions were identified to support continued use of the WHO Checklist beyond the trial period.

### Recommendations.

- The local implementation team and research team need to be aligned through a standardized strategy with clear roles and scope of work to guide intervention implementation. This is especially important in anticipating and planning for staff turnover depending on the length of the trial.
- Consider including front-line users of the intervention in addition to local leadership on the implementation team to maximize buy-in and integration of the intervention into existing workflows.
- Because implementation challenges requiring adaptation may arise, it is important to budget and plan sufficient time for the early formative work in developing the implementation strategy for a complex intervention.
- Recognize and work to achieve a balance between the science and art of implementation within the confines of the trial design.
- The implementation team should be embedded in the local context as much as possible to facilitate troubleshooting and ensure the intervention is implemented with fidelity.
- Measure the fidelity to the intervention implementation strategy during the trial or evaluation.
- Consider whether refresher training is needed for the implementation team, depending on staff turnover, fidelity to implementation strategy, and duration of the study.

### Data Quality Assurance Systems

The BetterBirth Trial achieved high ascertainment of health outcomes through a call center that successfully followed up with the majority of women (89,858/91,770, 97.9%) in addition to field workers who followed up with the remaining 1.6% (n=1,447). Only 0.5% (n=465) of enrolled women were lost to follow-up. (14) The Data Quality Monitoring and Improvement System was a robust, multicomponent system that ensured high-quality data throughout the BetterBirth Trial. The 5 components were: 1) monitoring and evaluation expert team who supported data quality assurance, 2) standard operating procedures for data collection, 3) training for data quality, 4) electronic data collection and reporting system, and 5) data quality assurance protocol, including data collection audits, rapid data feedback, and supportive supervision. (15)

### Recommendations.

- Build a data quality assurance team with data science expertise and a data quality assurance strategy, including continuous data cleaning to identify potential problems that can be addressed.
- Invest in a system to minimize loss to follow-up and maximize data quality and budget for this appropriately.

- Adapt data collection and follow-up methods to be contextually appropriate and culturally sensitive.
- Develop a rigorous process for designing and piloting data collection instruments, keeping in mind the purpose of collecting each variable and potential linkages required among multiple data sets.
- Ensure that there are fail-safe procedures for data backup and protection.

### Dissemination Strategy

Once preliminary data analyses were complete, the BetterBirth team worked through a systematic process to refine analyses and develop key messages from the findings. First, the BetterBirth team presented the results among the internal partners, including the governments of India and Uttar Pradesh, Ariadne Labs, the Scientific Advisory Committee, and the Bill and Melinda Gates Foundation. We also partnered with the communications specialists at Ariadne Labs to develop a dissemination strategy for the results of the trial. Study participants, including facility and district staff and leadership, learned about the results at district-level meetings across Uttar Pradesh. Then, the BetterBirth team disseminated the results globally and targeted diverse audiences, such as academics, program implementers, and clinicians. Some examples include a keynote address and panel discussion at the Royal College of Obstetricians and Gynecologists World Congress; peer-reviewed publications; grand rounds and lectures at universities; podcasts and webinars; media interviews and blogs; and donor reports. In addition, the BetterBirth team worked with WHO to build a checklist collaborative between 2012 and 2015. This collaborative included 34 groups in 29 countries that implemented the WHO Checklist in 234 sites. Some of these groups conducted feasibility and evaluation studies of their adaptation and implementation of the WHO Checklist (16) and trial results were shared with this group through a technical consultation in Sri Lanka. (17)

### Recommendations.

- Partner with a communications specialist and graphic designer to develop messaging from the trial results and roll out a dissemination strategy to reach different audiences, including the study participants. The dissemination method will depend on the audience and need to be tailored to the appropriate context. It may be valuable to prepare and pilot specific presentations depending on the audience.
- Consider whether some data analyses could be completed for earlier dissemination while waiting for the main trial results.
- Building early global collaborations before and during the trial may be beneficial in maximizing impact.

## CONCLUSIONS

We believe this roadmap of lessons learned in the BetterBirth Trial can aid the design, implementation, and dissemination of future large-scale studies of complex interventions. Recommendations include partnering with multidisciplinary collaborators, developing a theory of change, investing in formative work and pilot testing, building an intervention implementation strategy, creating data quality assurance systems, and partnering with communications specialists in a dissemination strategy. It is important for the research community to consolidate lessons learned from other similar trials and use (or create if needed) the standard frameworks for these large-scale trials with complex interventions so that best practices are identified and implemented. One example of such a framework is the Standards for Reporting Implementation Studies, which consist of a checklist for reporting key elements from the intervention and implementation strategy in implementation studies. (18) With the growth of translational research between clinical effectiveness and implementation in diverse global populations, advancing the field of large-scale studies with complex interventions will require guidance around intervention design and implementation strategy.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the issues in the organization of perinatal care (eg, regionalization, transport, practice guidelines, benchmarking data, quality improvement).
- Understand the strengths and limitations of randomized controlled studies.

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## Historical Perspectives: Lessons from the BetterBirth Trial: A Practical Roadmap for Complex Intervention Studies

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# Primary Immunodeficiency in the NICU

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## Practice Gap

Early detection of primary immunodeficiency disorders (PIDs) improves clinical outcomes. Various PIDs can present in the neonatal period; however, many neonatologists are not familiar with the breadth of these disorders and their presenting features.

## Abstract

Primary immunodeficiency disorders (PIDs) are **genetic diseases** that lead to increased susceptibility to infection. Hundreds of PIDs have now been described, but a select subset commonly presents in the neonatal period. Neonates, especially premature newborns, have relative immune immaturity that makes it challenging to differentiate PIDs from intrinsic immaturity. Nonetheless, early identification and appropriate management of PIDs are critical, and the neonatal clinician should be familiar with a range of PIDs and their presentations. The neonatal clinician should also be aware of the importance of consulting with an immunologist when a PID is suspected. The role of newborn screening for severe combined immunodeficiency, as well as the initial steps of laboratory evaluation for a PID should be familiar to those caring for neonates. Finally, it is important for providers to be familiar with the initial management steps that can be taken to reduce the risk of infection in affected patients.

**AUTHOR DISCLOSURE** Dr O'Connell has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

ALPS	autoimmune lymphoproliferative syndrome
CGD	chronic granulomatous disease
CID	combined immunodeficiency
DOCK8	dedicator of cytokinesis 8
HIES	hyper IgE syndrome
Ig	immunoglobulin
IL	interleukin
IPEX	immunodeficiency polyendocrinopathy X-linked
KREC	$\kappa$ -deleting recombination excision circle
LPS	lymphoproliferative syndrome
NK	natural killer
PDA	patent ductus arteriosus
PID	primary immunodeficiency disorder
SCID	severe combined immunodeficiency
SCT	stem cell transplantation
TREC	T-cell receptor excision circle
WAS	Wiskott-Aldrich syndrome
WBC	white blood cell
XLP	X-linked lymphoproliferative disease

## Objectives After completing this article, readers should be able to:

1. Recognize neonatal signs and symptoms that warrant consideration of a primary immunodeficiency disorder.
2. Explain T-cell receptor excision screening and when it is suggestive of severe combined immunodeficiency.
3. Describe the importance of early detection of primary immunodeficiency disorders.

## THE CASE

A 17-day-old male infant born at 24 5/7 weeks' gestation was transferred to a different NICU for planned patent ductus arteriosus (PDA) ligation, which was



not available at the referring institution. The birth was secondary to spontaneous premature rupture of membranes with unstoppable preterm labor. The mother had started receiving betamethasone, but the course was not completed before delivery. The infant's Apgar scores at delivery were 1, 3, and 3 at 1, 5, and 10 minutes, respectively. The postnatal course was notable for persistent hypotension requiring intermittent pressors and hydrocortisone, which was continued at the time of transfer. There was a history of pneumothorax and pulmonary hemorrhage, which had stabilized. He also sustained an intestinal perforation at 14 days of age requiring peritoneal drain placement. Echocardiography on the day of transfer showed a large PDA with holosystolic flow reversal in the aorta, so the decision was made to transfer him for surgical ligation.

The patient was transferred on stable ventilator settings and had a PDA ligation on the second day after admission. The procedure was tolerated well with no complications. About 1 week later, he had increasing abdominal girth and underwent a peritoneal drain revision. However, despite this treatment, he continued to have abdominal distention and ultimately underwent an exploratory laparotomy with small bowel resection at 6 weeks of age, which demonstrated multiple perforations. He required a second surgical revision 1 week later with silo placement. He suffered from severe edema and eventually the silo was taken down and a vacuum dressing was placed. Meanwhile, he also developed *Candida parapsilosis* bacteremia resulting in 21 days of treatment with amphotericin B at 2 months of age. The abdomen was finally closed at 3 months of age. At 4 months of age, he became hypotensive and developed signs of sepsis with blood cultures that grew *Klebsiella pneumoniae* and a urine culture that grew more than 100,000 colony-forming units per milliliter of *C parapsilosis*. Despite broad-spectrum antibiotics, he developed progressive tissue necrosis with severe lactic acidosis. Care was redirected toward comfort measures and the patient died of fulminant sepsis.

While in the second NICU, the patient had several newborn screens that showed **absent T-cell receptor excision circle (TREC) levels**. However, he had a normal TREC level on his initial newborn screen 1 week after birth, which typically does **not** suggest severe combined immunodeficiency (SCID). Immunology was consulted at 2.5 months of age because of the absent TRECs and, at that time, his T-cell lymphopenia with a total white blood cell (WBC) count was  $7,850/\mu\text{L}$  ( $7.85 \times 10^9/\text{L}$ ), absolute **lymphocyte count was  $490/\mu\text{L}$  ( $4.9 \times 10^9/\text{L}$ ; normal  $2,340\text{--}5,450/\mu\text{L}$  [ $2,340\text{--}5,450 \times 10^9/\text{L}$ ]), and low total  $\text{CD4}^+$  and  $\text{CD8}^+$  T-cell counts**. He was critically ill in the setting of the abdominal surgeries, and had significant edema and third-spacing, so the immunology

team recommended performing functional immune studies once the patient was more stable. Approximately 1 month later, the patient had clinically improved and had a normal WBC count of  $9,630/\mu\text{L}$  ( $9.6 \times 10^9/\text{L}$ ) and an absolute lymphocyte count of  $2,370/\mu\text{L}$  ( $2.3 \times 10^9/\text{L}$ ), which was in the normal range. Therefore, immune testing and immune function testing were repeated, which demonstrated a **significant T-cell lymphopenia and severely abnormal T-cell function testing with deficient response to mitogens**, consistent with immunodeficiency. Unfortunately, during this week of testing the patient developed sepsis and died.

The case illustrates the complexities of detecting immune abnormalities in the neonatal population. It is particularly challenging in preterm infants, who have immature immune systems. Preterm infants have **impaired innate and adaptive immune responses** compared with term infants, specifically as a result of diminished neutrophil function, decreased production of antimicrobial cytokines, Th17 immune skewing, and impaired regulatory T-cell function. (1)(2)(3)(4)(5)(6) Nonetheless, being born prematurely does not exclude the possibility of also having a genetic immunodeficiency. However, given a high number of false-positive TREC screens in neonates, there is potential for "alarm fatigue" when it comes to preterm infants, so that abnormal results may be written off as secondary to illness or prematurity. Therefore, diagnosing a primary immunodeficiency disorder (PID) in this population requires special consideration from clinicians. This review will focus on the clinical presentation and initial management of those PIDs that are most likely to present in the neonatal period.

## EPIDEMIOLOGY

PIDs are genetic inherited disorders that cause defects in the immune system, predisposing patients to infections. They are to be distinguished from secondary immunodeficiency, which is an immune deficit secondary to another cause, such as with **human immunodeficiency virus infection or chylothorax**. At the beginning of 2018, more than 350 genetic causes of these inborn errors of immunity had been recognized, (7) with additional disorders continuing to be identified. Several of these disorders commonly present in the neonatal period with frequencies high enough that practicing neonatologists should encounter them at some point during their career. For example, the incidence of SCID is 1 in 33,000 births, (8) so with roughly 4 million annual births in the United States, this would suggest that as many as 120 infants are born with SCID every year. For

comparison, the incidence of double-outlet right ventricle is similar to that of SCID, just one type of PID. If prematurity and immunodeficiency are independent events, with a 12% incidence of prematurity, about 10 preterm infants would be born with SCID every year in the United States.

## PRESENTATION

### Infection

PIDs are typically characterized by their susceptibility to infection, therefore serious infections are a major feature of neonatal PID. To aid providers in identifying clinical features that might help to distinguish PIDs from other cases of infection, a list of clinical “warning signs” for PIDs has been developed. (9) The presentation of PIDs in the neonatal period requires special consideration, however, owing to differences in development and management that are specific to neonates. Neonatal sinuses are underdeveloped and sinusitis may not be a prominent symptom. (10) Otitis, pneumonias, and sepsis may occur, and are red flags in otherwise healthy neonates, but in premature or already hospitalized critically ill neonates, it may be difficult to differentiate between primary genetic susceptibility and susceptibility related to mechanical ventilation, indwelling central lines, and secondary immunodeficiency. Likewise, the need for hospitalization cannot be a distinguishing feature prompting further PID consideration because **any fever in a neonate younger than 30 days warrants a full sepsis evaluation and admission to the hospital according to widely accepted practice guidelines**. (11)(12) Therefore, the neonatal population requires the very highest scrutiny to detect PIDs in the neonatal period. A list of PID warning signs, modified to better suit the neonatal population, is provided in Table 1.

Infectious considerations for making a diagnosis of PID include the **type and severity** of infection, as well as the **specific microbe** causing the infection. The most common sites of infection vary with the particular type of PID; indeed, the presenting site of infection can be used to narrow down the diagnostic category (Table 2). Generally speaking, patients with combined immunodeficiencies will have increased susceptibility to viral, bacterial, and fungal infections because of lack of both cellular and humoral immunity. Patients with **humoral immunity** tend to present with sinopulmonary infections. Those with **primary granulocyte disorders** have sinopulmonary infections and abscesses. In addition to the site and severity of infection, the microbes causing the infection should also trigger consideration for a PID. Sepsis caused by an unusual pathogen is concerning.

### Rash and Eczema

Several categories of PIDs feature rashes from the neonatal period. A particularly suspicious finding is the presence of **erythroderma** in a neonate. **Staphylococcal scalded skin syndrome** can present in this age group and should be ruled out. **Omenn syndrome**, which is a type of “leaky” SCID in which some autoreactive T cells are still produced, leading to autoreactive properties, is one potential cause of erythroderma that can be present from birth. (13)(14) Other PIDs that can prominently feature eczema, including immunodeficiency polyendocrinopathy X-linked (IPEX), Wiskott-Aldrich syndrome (WAS), and hyper immunoglobulin (Ig) E syndrome (HIES), can also present with a significant rash in the neonatal period, though these are typically not present at the time of birth. (15)(16) (17)(18)

### Autoimmunity

Although many PIDs feature an increased incidence of autoimmunity over the lifetime of the patient, a smaller group of PIDs can present with autoimmunity in the neonatal period. Patients with IPEX can present with autoimmune symptoms in the neonatal period, most typically **insulin-dependent diabetes and/or autoimmune enteritis**. (19)(20)(21) Patients with interleukin (IL)-10 deficiency and IL-10 receptor deficiency can also present with enteritis in the neonatal period. (22) Lymphoproliferative syndrome (LPS)-responsive and beige-like anchor protein deficiency has been associated with neonatal-onset diabetes as well. (23)

### Food Allergy and Asthma

Some PIDs are prominently associated with the development of atopic symptoms such as eczema, asthma, and food allergy. These include dedicator of cytokinesis 8 (DOCK8) deficiency and WAS, but this can also occur in other PIDs such as combined immunodeficiency (CID). (24)(25) These symptoms tend to develop beyond the neonatal period, however, likely owing to the time needed for the immune system to become sensitized to various allergens.

### Hydrops Fetalis

Hydrops is not commonly considered a feature of PIDs, however, there have been anecdotes of a PID being diagnosed in patients with a history of hydrops. Several cases of hydrops with underlying diagnoses of IPEX have been described. (26)(27) Prenatal hydrops has also been found in a case of X-linked inhibitor of apoptosis deficiency, which causes X-linked lymphoproliferative disease (XLP) type 2

TABLE 1. **Warning Signs of Primary Immunodeficiency Disorder in the Neonatal Period**

<b>Infections with unusual pathogens</b>
Fungi
Mycobacteria
<i>Nocardia</i> sp.
<i>Serratia marcesans</i>
<i>Burkholderia cepacia</i>
<i>Salmonella</i> sp.
<i>Cryptococcus</i> sp.
<b>Atypical types of infection</b>
Abscesses
Omphalitis
Encephalitis
Meningitis
Pneumonia without history of bronchopulmonary dysplasia
<b>Need for prolonged antibiotic course</b>
<b>Recurrent or repeated infections</b>
<b>Recalcitrant thrush</b>
<b>Erythroderma</b>
<b>Severe eczema</b>
<b>Neonatal-onset diabetes</b>
<b>Chronic diarrhea</b>
<b>Colitis</b>
<b>Failure to thrive</b>
<b>Prenatal history of unexplained hydrops</b>

Derived from "10 Warning Signs of PI" developed by the Jeffrey Modell Foundation. Available at <http://www.info4pi.org/library/educational-materials/10-warning-signs>. Accessed November 20, 2018.

(28). Hydrops without a clear etiologic factor should prompt consideration of further genetic testing.

#### Hepatosplenomegaly and Hemophagocytic Lymphohistiocytosis

**Hepatosplenomegaly** can be a presenting feature of neonatal PIDs, especially lymphoproliferative disorders such as autoimmune lymphoproliferative syndrome (ALPS). (29) Other PIDs, especially XLP types 1 and 2, may feature hepatosplenomegaly in infancy but have not been widely described in the neonatal period. Hepatosplenomegaly can present in conjunction with hemophagocytic lymphohistiocytosis, which has also been described in the neonatal period

in association with chronic granulomatous disease (**CGD**). (30)

#### PIDs COMMONLY PRESENTING IN THE NEONATAL PERIOD

##### Severe Combined Immunodeficiency

**SCID is** one of the most severe clinical presentations of PIDs. This disorder is a constellation of many different genetic defects that all result in an **inability to activate antigen-specific T cells**. Defects that lead to SCID can be located anywhere along the pathway of T-cell receptor gene rearrangement, production, antigen binding, costimulation, or downstream signaling (Fig).

TABLE 2. Major Classifications and Infectious Features of PIDs

CATEGORY	PRIMARY DEFECT	INFECTIONS	MAIN PATHOGENS
SCID	T cells, B cells, $\pm$ NK cells	Any site	Viruses, bacteria, fungi
CID disorders	T cells, B cells	Any site	Viruses, bacteria, fungi
B-cell disorders	B cells, immunoglobulins	Pneumonia, otitis, sinusitis	Encapsulated bacteria, enteric viruses
Neutrophil	Neutrophils	Skin infections, otitis, pneumonia, sinusitis	Bacteria

CID=combined immunodeficiency; NK=natural killer; PID=primary immunodeficiency disorder; SCID=severe combined immunodeficiency.

The most common form of SCID is **X-linked SCID**, caused by a mutation in the T-cell IL-2 receptor  $\gamma$  subunit. In addition to being important for downstream signal propagation through the T-cell IL-2 receptor, this cytokine receptor subunit is also important for IL-15 receptor function on natural killer (NK) cells and for responses to several other cytokines (IL-4, IL-7, IL-9, IL-21) that are important in T-cell and B-cell maturation. Therefore, a defect in this gene leads to diminished T cell, B cell, and NK cell numbers and function. An inability to signal via the T- or B-cell antigen receptor leads to **defective replication** of T and B cells because of a lack of antigenic signal, which is why these disorders uniformly feature decreased numbers of T and/or B cells and NK cells, and do not just impair function.

**Infections** in patients with SCID can occur in **any site**, and can be **viral, bacterial, or fungal**. Because SCID is such a severe disorder, and because performing stem cell transplantation (SCT) before a patient's first infection drastically improves outcomes, newborn screening techniques have been developed to identify SCID as early as possible. See the section on "Screening for PIDs" for more information.

### Combined Immunodeficiency Disorders

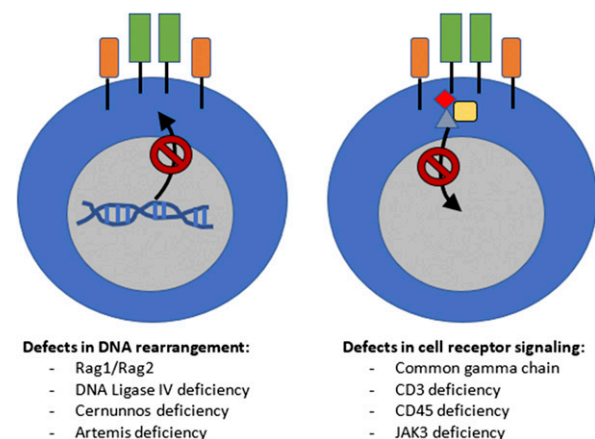
CID disorders feature **defects in both the T- and B-cell compartments** and have the potential to cause the same diverse types of infections as SCID. However, they are distinguished from SCID because they do **not carry the same risk of mortality in the first year after birth if untreated**. (31)(32) There is genetic overlap between SCID and CID, with some gene mutations causing either disorder because of differences in functional consequences of the mutations. Because these disorders are not as severe, they present in the neonatal period **less commonly than SCID**. Select CID disorders most likely to present in the neonatal period are as follows:

**Hyper IgM Syndrome.** This results primarily from **defects** in either **CD40** or the **CD40 ligand**, which blocks the stimulation required for B cells to switch from production of IgM to other subclasses, hence the moniker *hyper*

*IgM syndrome*. (32)(33) In addition, these molecules are needed for T-cell memory responses, so that mutations cause a CID rather than merely a humoral immune defect.

**Wiskott Aldrich Syndrome.** WAS is a result of mutations in WAS protein (WASp) that is important for **cell membrane interactions with the actin cytoskeleton**. (34) Loss of function of this protein results in impaired response to cell receptor stimulation for T and B cells, and defective cellular migration, which leads to a comprehensive immunodeficiency affecting most types of **lymphocytes**. Because of the importance of WASp in **megakaryocyte maturation**, patients also have **microthrombocytopenia**, which can cause clinical bleeding that may be the presenting feature in neonates.

**Hyper IgE Syndrome.** HIES is caused by mutations in STAT3, which is required for Th17 CD4<sup>+</sup> subset development. Affected patients therefore have impaired Th17



**Figure.** Problems that cause severe combined immunodeficiency (SCID) and example of genetic disorders. Left, representation of a cell with a defect in DNA rearrangements, which **prevents the T-cell receptor on the cell surface from being encoded normally**. This results in a lack of surface expression of a normal number and diversity of T-cell receptors, leading to impaired production of T cells. Right, representation of a cell with normal T-cell receptors, but impairment in signaling of the T-cell receptor complex because of an abnormal costimulatory molecule or intracellular protein required for propagating the T-cell receptor stimulation. Some causes of SCID, such as **adenosine deaminase deficiency**, lie outside these mechanisms.

responses and a concomitant increase in Th2 responses, which are strongly linked to **atopy**. Because of the diminished Th17 response, affected patients are susceptible to fungal and bacterial infections. They also have very elevated IgE production, which seems to be linked to a direct effect of STAT3 deficiency on B-cell class switching. (35)

**DOCK8 Deficiency.** DOCK8 is required for migration of CD8<sup>+</sup> T cells into collagen, therefore these patients are unable to mount a response to skin infections. (36) Affected patients also have **very high total IgE levels and eosinophilia**. (37) They may present in the neonatal period with persistent skin infections including with ***Staphylococcus***. Severe eczema and a predisposition to atopic diseases are characteristic. (37)

**DiGeorge Syndrome.** Most commonly, **gene deletions at 22q11.2** cause DiGeorge syndrome. (38) The phenotype is the result of **abnormal development of the pharyngeal structures**, and affected patients have varying degrees of defects in the **velopharyngeal tissue, thymus, and parathyroid glands**, as well as **cardiac conotruncal defects**. Owing to a range of thymic hypoplasia to aplasia (complete DiGeorge), patients can present with SCID or CID. **Thymic transplantation** is a therapeutic option for complete DiGeorge syndrome. (39)

### B-Cell Disorders

Disorders of B cells lead to defects in **humoral immunity**, owing to the primary role of B cells in generating antibodies. These antibodies are particularly important for protection against **encapsulated bacteria**. Typical symptoms of B-cell disorders are **otitis, sinusitis, and pneumonia**. Because most infants are born with **maternally derived IgG**, which is the only antibody subclass that crosses the placenta, it is not common for humoral immunodeficiency to present in the neonatal period. Maternal IgG levels tend to taper off around **6 months** of age in term infants, at which point B-cell disorders may become symptomatic. Premature infants may present **earlier**, owing to a lack of complete maternal antibody transfer, because **peak maternal IgG transfer** occurs **after 34 weeks** of gestation, (40) resulting in lower peak IgG levels than term infants. (41) However, the age at diagnosis in patients with no family history is usually well beyond the neonatal period.

**X-linked agammaglobulinemia** is caused by deficiency of **Bruton tyrosine kinase**, which is required for B-cell precursor development. (42)(43) Affected **males** have diminished B cells and decreased levels of **all** classes of immunoglobulins, resulting in recurrent infections with **encapsulated bacteria**. X-linked agammaglobulinemia rarely presents clinically in the neonatal period; however,

the recent development of  $\kappa$ -deleting recombination excision circle (KREC) screening (see “Screening for PIDs”) may ultimately lead to more neonatal diagnoses, so it is prudent for neonatal clinicians to be aware of this condition.

### Neutrophil Disorders

Neutrophils are critical for **peripheral response to bacterial infection**, and neutrophil disorders are typically associated with the **absence of pus** production at the site of an infection. These disorders predispose patients to **skin and sinopulmonary infections**.

**Chronic Granulomatous Disease.** CGD is a severe PID caused by defects in any of the components of the **oxidative phosphorylation complex**. (44) This results in impaired ability of neutrophils to kill phagocytosed bacteria or fungi and can present with severe infections in the neonatal period. CGD is best screened for by assessing the **oxidative burst of neutrophils** by using the **dihydrorhodamine test**.

**Chediak-Higashi Syndrome.** Although extremely rare, the unique physical examination findings of Chediak-Higashi syndrome are notable in the neonatal setting. The mutations of the *CHS1/LYST* gene lead to abnormal lysosomal trafficking that results in **neutrophil dysfunction, oculocutaneous albinism**, and **easy bruising and bleeding**. (45)(46) (47)

**Congenital Neutropenias.** These disorders, which include cyclic neutropenia, feature impaired development of neutrophils and an absolute neutrophil count persistently lower than **500/ $\mu$ L**. (48) In addition to therapies outlined here, patients may be treated with **granulocyte colony-stimulating factor**.

### Other Disorders

The grouping of these disorders is somewhat arbitrary in this review. Although some of them belong to larger subgroups, they are described together here to highlight those particular disorders most likely to present in the neonate.

**Toll-like Receptor 4 Pathway Disorders.** IL-1 receptor-associated kinase 4 deficiency and myeloid differentiation factor 88 deficiency lead to impaired toll-like receptor 4 pathway signaling, which is important in the detection of microbial lipopolysaccharide. (49)(50) They may present in the neonatal period with bacterial infections, which are mostly limited to *Staphylococcus aureus*, *Pneumococcus*, and *Pseudomonas aeruginosa* infections, which also tend to be common causes of nosocomial infections in the NICU. (51)

**Leukocyte Adhesion Disorder.** Leukocyte adhesion disorder has a low incidence compared with many other PIDs. Its relevance to the neonatal clinician is in the presentation,

which may feature omphalitis or delayed separation of the umbilical cord. (52) Leukocyte adhesion disorder has 3 subtypes, all involving abnormalities in integrin or selectin function, which leads to an inability of leukocytes to extravasate from the blood vessels. (53) This causes an elevated number of circulating leukocytes, such that WBC counts greater than  $50,000/\mu\text{L}$  ( $50 \times 10^9/\text{L}$ ) are common in these patients. Meanwhile, the leukocytes, particularly neutrophils, have difficulty making their way to the site of an infection, which causes a sterile pyuria, which can have a fulminant infection with a paucity of pus production.

**Autoimmune Lymphoproliferative Syndrome.** ALPS is considered a lymphoproliferative disorder. (54) Defects in Fas or Fas ligand are the main causes, and their absence results in a compromised apoptosis response in circulating lymphocytes, so that the lymphocyte compartment expands without restriction. (55) Clinically, this leads to splenic and hepatic enlargement. Cytopenias can result from bone marrow competition and from autoantibody production against both red cells and platelets. (56) ALPS can present in the neonatal period.

### Autoinflammatory Diseases

The past decade has resulted in an increased awareness of autoinflammatory disorders, which are characterized by **genetic abnormalities** leading to inappropriate activation of the inflammatory system. The inflammatory pathway is differentiated from other immune pathways in that the hallmark of these disorders is an **inappropriate activation of microbe-sensing pathways**, whereas PIDs typically reflect a hypofunctioning immune response. Patients typically present with **fevers**, **joint inflammation**, and **rash**. Other distinguishing features depend on the particular disorder. These conditions have been reviewed elsewhere. (57)(58) (59)

### SCREENING FOR PIDs

As of 2018, newborn screening for SCID is available across 94% of the United States, with state screening programs in Alabama, Indiana, and Louisiana planning to begin screening by the end of 2018, making US screening universal. (60) Many other countries are also screening for SCID. Screening for SCID relies on **polymerase chain reaction technology** and takes advantage of the process of **germline gene rearrangements**, which are unique to T and B cells. To create a robust, diverse repertoire of T-cell receptors, clusters of genes that encode variable (V), joining (J), and diversity (D) segments are spliced and recombined so that each individual cell has only 1 of each type of gene segment.

In the process of splicing these segments together, short TRECs are created, which are circular and contain a stable sequence that can be detected by primers. Using TREC-specific primers, the number of TRECs present in a sample can be determined using quantitative polymerase chain reaction.

As of July 2018, SCID screening has not missed any cases of typical SCID, correlating with a sensitivity of 100%. (61) Specificity is not 100%, owing to various other conditions that can lead to an abnormal finding on the TREC screen. These include other forms of PIDs, idiopathic T-cell lymphopenia, prematurity-related immune immaturity, chylothorax, and genetic syndromes, among others. Because prematurity itself can cause low TREC scores, it has been suggested that preterm infants undergo repeated TREC assays before being referred for additional diagnostic studies. (62) Indeed, this would help to increase the positive predictive value of an abnormal TREC screen in premature infants; however, the clinical history should also be kept in mind and a suggestive clinical history should prompt consideration of flow cytometry studies without waiting for a repeat TREC screen.

Similar technology is available to screen for B-cell disorders, using KRECs. KREC screening is available in several European countries. (63) Although the overall mortality associated with B-cell disorders is lower than that seen in SCID, patients with B-cell disorders still have increased lifetime mortality and serious morbidity, which might be improved by early detection and implementation of prophylactic therapies before the onset of infection.

### EVALUATION

Whenever a PID is considered, a specialist trained in clinical immunology should be consulted. In regions that do not have immediate access to a local immunologist, a free consultation with an immunologist can be arranged through the Immune Deficiency Foundation (<https://primaryimmune.org/healthcare-professionals/idf-consulting-immunologist-program>). Basic screening should include a **complete blood cell count, lymphocyte subset panel, and antibody levels**. A **dihydrorhodamine assay** should be added if neutrophil disorders are suspected. These blood tests can be performed using a total volume of approximately 1.5 to 2 mL at a skilled facility.

Blood volumes required for further immune tests can be problematic in neonates, because many tests typically involve extensive flow cytometry or cell stimulation protocols, for which blood volumes of 5 to 10 mL are typically used in adults. Additional levels of diagnostic testing, including



T-cell function tests, extended cell phenotyping, and genetic testing should be undertaken in consultation with the clinical immunologist to maximize clinical symptom-directed testing.

Newer technologies are beginning to be applied in the diagnosis of PIDs. Next-generation sequencing panels to evaluate for known mutations have improved speed and specificity in the diagnosis of PIDs versus the conventional flow cytometry plus Sanger sequencing approach. (64)(65)(66) It is hoped that this will lead to faster diagnosis and time to treatment in the future. Some centers have begun to apply whole exome sequencing for suspected PIDs without a causative mutation identified. (67) Indeed, exome sequencing is being used more commonly in the neonatal population for suspected genetic disease. (68)(69) The Clinical Immunology Society recently published a comprehensive guideline for genetic evaluation of PID. (70)

## MANAGEMENT

Specific management for patients with PIDs depends on the specific PID. In disorders with severe clinical effects such as SCID, WAS, CGD, DOCK8, and ALPS, SCT has been used. Gene therapies are also being evaluated in clinical trials. The mainstay of therapy for most PIDs involves preventing infection. This can be in the form of medications or behavioral adaptations (7)(32)(48)(71).

### Infection Prevention

**Precautions.** Any hospitalized patient who is being evaluated for a possible diagnosis of SCID should be moved to an isolation room. Neonates who are at home should be isolated from visitors and young children who are more likely to be reservoirs for infection, and good hand hygiene should be used.

**Transfusion Considerations.** It is standard to give neonates leukoreduced, irradiated products when performing transfusions. This is especially critical for patients with SCID or CID, because any residual leukocytes in a transfusion might lead to graft-versus-host disease in these patients.

**Vaccinations.** Patients with SCID or CID, or those being considered for T-cell lymphopenia disorders, **should not be given live vaccines, whether viral or bacterial**, because these vaccinations can lead to disseminated infection in the immune compromised. This includes **pavilizumab**.

**Antimicrobials.** For patients with SCID, CID, or antibody-mediated PIDs, **bacterial prophylaxis should be initiated**.

**Amoxicillin** is the most commonly used medication for neonates. Amoxicillin-clavulanate, azithromycin, and trimethoprim-sulfamethoxazole (preferably >2 months of age) are other options. For patients with SCID, *Pneumocystis jirovecii* prophylaxis with **trimethoprim-sulfamethoxazole** should be initiated. Antifungal therapy is indicated for patients with SCID and CGD.

**Immunoglobulin.** This is the **mainstay of therapy** for humoral defects. In addition, patients with SCID and CID are given maintenance Ig treatments. Ig can be given in intravenous and subcutaneous preparations.

**Interferon.** Interferon therapy has been shown to prevent infections in patients with CGD and should be started as part of their prophylactic regimen after diagnosis.

## Definitive Therapies

**SCT** is recommended for many categories of PIDs with elevated morbidity and mortality, especially SCID. SCT is most commonly performed with matched allogeneic hematopoietic stem cells, though umbilical cord blood-derived cells can be used. SCT carries its own risks and morbidities, and therefore it is not recommended for every type of PID. The timing and logistics of SCT are beyond the scope of this review, however, the interested reader can refer to the indicated references for more information. (72)(73)(74)(75)

**Gene therapy** is emerging as a therapeutic alternative in patients who would otherwise qualify for SCT but for whom no appropriate donor is available. Gene therapy trials have been completed or are underway for WAS, (76)(77) CGD, (78)(79)(80)(81) and some types of SCID. (82).

## IMPORTANCE OF EARLY DETECTION

Early diagnosis and definitive treatment for SCID has been shown to improve patient survival. (83) It has been shown that SCT or gene therapy before a major infection minimizes complications and maximizes the chance of therapeutic success. (84) This is true for other types of neonatal-onset PIDs as well. (85) The importance of identifying and detecting PIDs as early as possible makes it critical for the neonatal clinician to be aware of the breadth and scope of disease, as well as to be familiar with initial management and reasons for referral to an immunologist. Furthermore, even in situations in which infants are already too sick to recover (such as in the case described herein), having the awareness to consider PIDs may help to inform parents of potential genetic susceptibilities that may be of importance to planning future pregnancies.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical features and differential diagnosis of neonates with immune deficiencies.
- Know the initial screening tests and subsequent specific diagnostic tests used to evaluate neonates with possible defects in host defense mechanisms.

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1. An infant's newborn screening result comes back positive and indicates severe combined immunodeficiency. Which of the following correctly describes this condition?
  - A. The disorder is primarily caused by the dysfunction of neutrophils.
  - B. Infections in patients with this condition can be viral, bacterial, or fungal.
  - C. The most common form is inherited in an autosomal recessive fashion.
  - D. This disorder leads only to infections isolated to the mucous membranes.
  - E. A common finding will be increased numbers of T and B cells, with variable function.
2. An infant is diagnosed with a primary immunodeficiency disorder after persistent skin infections. The patient also has severe eczema and very high total immunoglobulin (Ig) E levels and eosinophilia. Which of the following is the most likely diagnosis?
  - A. Hyper IgM syndrome.
  - B. Wiskott-Aldrich syndrome.
  - C. Hyper IgE syndrome.
  - D. Deducator of cytokinesis 8 deficiency.
  - E. DiGeorge syndrome.
3. A newborn is noted to have a skin infection, oculocutaneous albinism, and easy bruising. Which of the following is likely to be present in this disorder?
  - A. Abnormal lysosomal trafficking leading to neutrophil dysfunction.
  - B. Cyclic neutropenia.
  - C. A deficiency of Bruton tyrosine kinase.
  - D. Thymic hypoplasia and hypocalcemia.
  - E. Extremely elevated IgM and IgE production.
4. A preterm newborn of 32 weeks' gestational age has a positive newborn screening result for severe combined immunodeficiency. Which of the following statements regarding this screening test is correct?
  - A. The sensitivity of this screening test is less than 75%, making clinical suspicion during the first year an important aspect of timely diagnosis.
  - B. The screening test is not 100% specific, with other conditions that can lead to an abnormal screen, such as idiopathic T-cell lymphopenia and prematurity-related immune immaturity.
  - C. The test relies on mass spectrometry to detect levels of the SC8 protein.
  - D. Prematurity can lead to spuriously high T-cell receptor excision circles, leading to high false-negative rates in this group.
  - E. Diagnostic testing should wait until the patient is 6 months old and after administration of the usual immunization schedule, including palivizumab.
5. You are treating a patient with severe combined immunodeficiency. The patient was identified on newborn screening and has yet to develop a serious infection. Which of the following is an appropriate aspect of management for this patient?
  - A. The patient should receive live vaccines earlier than the recommended schedule to boost immunity before school age.
  - B. If requiring a transfusion, the patient should receive leukocyte-enriched blood to facilitate immune function.
  - C. The most appropriate prophylaxis for pneumocystis is ciprofloxacin.
  - D. Stem cell transplantation is reserved for patients who have had at least 3 severe infections requiring hospitalization.
  - E. Bacterial prophylaxis with an antibiotic such as amoxicillin should be initiated.

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# Perinatal HIV Transmission: Missed Opportunities and Proposed Solutions

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## Education Gaps

While there has been tremendous progress in the goal of eliminating perinatal human immunodeficiency transmission, there are still some areas for improvement. Using case-based examples, this review will provide context for specific missed opportunities in the prevention of human immunodeficiency transmission.

## Abstract

Much progress has been made in the elimination of perinatal human immunodeficiency virus (HIV). Since the 1980s, the transmission rate from pregnant women to their children has dropped from approximately 25% to less than 1% in resource-rich areas. Routine HIV testing in pregnancy, the introduction of multidrug antiretroviral therapy for pregnant women, and the recognition that HIV viral load directly correlates with viral transmission have all led to the elimination of perinatal HIV. However, there are still missed opportunities that could further minimize transmission.

## Objectives After completing this article, readers should be able to:

1. Describe current guidelines for perinatal human immunodeficiency virus testing and management.
2. List current opportunities to further decrease the perinatal transmission of human immunodeficiency virus.

**AUTHOR DISCLOSURE** Drs Shihan, Arsenault, and Secord have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

ART	antiretroviral therapy
CDC	Centers for Disease Control and Prevention
HIV	human immunodeficiency virus
MTCT	maternal-to-child transmission

## PERINATAL HIV TRANSMISSION

In 1982, Ayre Rubinstein, MD, from the Bronx, NY, submitted a case series of several infants suspected to have perinatally acquired human immunodeficiency virus (HIV). The report was rejected by the American Academy of Pediatrics because the reviewers believed that this disease was restricted to homosexual men. The first cases of perinatal HIV were reported in the same year by the

Centers for Disease Control and Prevention (CDC). (1) Shortly after this report, a perinatal HIV epidemic ensued.

Perinatal transmission of HIV occurs when an HIV-infected woman transfers the virus to her child during pregnancy, labor, delivery, or breastfeeding. In 1996, the results of the pediatric acquired immunodeficiency syndrome clinical trial of zidovudine prophylaxis for infants were published. (2) The findings established that zidovudine given to HIV-positive pregnant women orally during the second and third trimesters of pregnancy, intravenously during labor and delivery, and by mouth to at-risk infants for 6 weeks resulted in a significant decrease in maternal-to-child transmission (MTCT) (2); early analysis revealed a decrease in transmission from 25% to 8%. (2) Shortly after this study, with the introduction of multiple new antiretrovirals and the ability to monitor HIV viral load, antiretroviral therapy (ART) became the standard of care for HIV-positive pregnant women to sustain their viral load at the lowest possible levels throughout pregnancy. This standard necessitated the offering of HIV testing to all pregnant women so that HIV-positive women could obtain treatment to decrease MTCT. Many HIV-positive women currently learn about their HIV-positive status through HIV testing during pregnancy. Multidrug ART throughout pregnancy in HIV-positive women or treatment as soon as HIV is diagnosed in pregnancy has resulted in a transmission of 1% or less in resource-rich areas of the world. If the mother's HIV viral load is low or undetectable, current guidelines recommend that the infant only receive oral zidovudine for 4 weeks. (3)

Within the United States (and internationally), there has been a striking decrease in the number of new perinatal HIV cases each year, with the CDC reporting a decrease from 1,650 new cases in 1991 to about 100 in 2015. (4) Since 2013, however, the rate of annual cases of MTCT has remained relatively steady. According to the CDC, 122, 137, 100, and 99 new cases were seen in 2013, 2014, 2015, and 2016, respectively. (5) A large retrospective analysis was published in *JAMA Pediatrics* in 2017, which presented statistics on the epidemiology of perinatal HIV cases between 2002 and 2013. (6) Of these 1,327 cases, a confirmed 41.8% of HIV-positive mothers had received their HIV diagnoses before pregnancy, 17.5% were confirmed as having been diagnosed during pregnancy, and 23.3% were confirmed as postdelivery diagnoses. This signifies that in some cases, the infant will become ill before the diagnosis of HIV is made.

Although lack of prenatal care may be a contributing factor to MTCT, it is certainly not the only factor. At least 30% of the 1,327 pregnant HIV-positive women were found to have received prenatal care, and a confirmed 38.7% of the women had received at least some ART during pregnancy.

(6) In 2016 in the United States, 65% of 99 perinatal HIV cases were born to black women, and 15% of the infants were born to Hispanic women, which may be a result of health care and social disparities in the United States. (7)

The most critical factors in avoiding MTCT are 1) identification of HIV infection, and 2) an effective treatment regimen that results in suppressed HIV viral load during pregnancy. However, other considerations, such as access and adherence to therapy, can affect whether or not this is achieved. Clearly, there are still barriers that prevent the complete elimination of perinatal HIV.

## CURRENT GUIDELINES FOR PERINATAL HIV TESTING AND MANAGEMENT

Current guidelines recommend that HIV testing of pregnant women (and any adult) begin with an antigen/antibody combination immunoassay (ie, fourth-generation HIV antigen/antibody assay). If this test is reactive, an HIV-1/HIV-2 antibody differentiation assay should be used. If the result of the combination immunoassay is positive but the differentiation testing result is nonreactive, an HIV nucleic acid test should be performed to diagnose acute HIV. If screening tests are not available, then testing should be based on the most sensitive test available. (8)

All pregnant women who test positive for HIV should start ART as soon as they are diagnosed to prevent vertical transmission and to protect their own health. Fortunately, ART is considered safe in pregnancy and is not associated with a higher risk of birth defects; however, as new therapies are introduced (which is frequent in HIV treatments), vigilance is necessary. There are no absolutely contraindicated ARTs during pregnancy at this time, but new agents exist, which have limited long-term data, and therefore need to be discussed and reviewed with the pregnant woman. For example, because the recent form of tenofovir (alafenamide) is relatively new, this medication is often substituted with the older form (disoproxil), which has been in use long enough to be considered safe in pregnancy. Resistance and tolerability are also important issues that must be discussed with the pregnant woman. Generally, the same regimens are used with pregnant women as the general population but they should be adjusted according to resistance results, adverse effects, drug interactions, and experience in using them during pregnancy.

A scheduled cesarean delivery to prevent MTCT of HIV is recommended for women with elevated HIV RNA levels (>1,000 copies/mL) or unknown viral loads near the time of delivery. If a pregnant woman has an HIV RNA load of more than 1,000 copies/mL, a cesarean section is recommended

during the 38th week of pregnancy and intravenous zidovudine should be administered in addition to the regular antepartum regimen. (3) Intravenous zidovudine is not indicated if the woman's HIV RNA level is less than 50 copies/mL. However, administering intravenous zidovudine when the HIV RNA level is between 50 and 999 copies/mL is a grey area and depends on the preference of the physician and patient. (3)

Virologic diagnostic testing is recommended (HIV DNA) for all infants with perinatal HIV exposure at the following ages: 14 to 21 days (another test is often done earlier, but should not be considered valid at <7 days), 1 to 2 months, and then at 4 to 6 months. However, virologic testing (HIV RNA for viral load) should be considered for high-risk infants. High-risk infants include those without prenatal care, those whose mothers did not receive the appropriate ART before delivery, and those whose mothers did not achieve viral suppression with treatment.

The specific prophylaxis regimen for the infant depends on maternal adherence to antepartum ART and achievement of maternal viral suppression. If there was sustained maternal viral suppression, then a 4-week zidovudine regimen is used. (3) If the infant is at high risk of acquiring HIV (as noted earlier), a 6-week course of zidovudine is advised as well as nevirapine in 3 doses (first dose within 48 hours, next dose 48 hours later, and third dose 96 hours after the second dose). In some high-risk cases, the clinician may opt to provide a 3-drug ART regimen for 28 days (postexposure prophylaxis) to the infant. (3)(9)

An infant with initial positive results on HIV viral tests (HIV DNA or HIV RNA) should start a treatment regimen of a 3-drug combination of ART; this is independent of infant viral load and presence/absence of clinical findings. The results of maternal HIV status should be documented in the newborn's record and communicated to the primary pediatric care clinician to ensure proper care of the infant. (10)(11)

## SCENARIOS OF PERINATAL HIV TRANSMISSION

Although perinatal HIV transmission is now very preventable with maternal ART for viral suppression and infant prophylaxis, cases of perinatal HIV are still seen each year, even in resource-rich settings such as the United States. The failure to prevent these cases results in a child being burdened with a lifetime of medications and treatment. Therefore, it is of utmost importance for medical professionals to investigate the causes of current perinatal HIV and to take action to prevent future missed opportunities. The following is a review of missed opportunities for HIV prevention in newborns. Why these cases were missed is

discussed as well as the potential steps that can be taken to decrease future occurrences.

### Case One

*Patient 1 is a small-for-gestational age male infant born at 36 weeks' gestation to a 19-year-old woman in an inner city in the Midwest with a high incidence of HIV. The woman had a negative first-trimester HIV test result. The infant suffered from anemia and thrombocytopenia and had a germinal matrix hemorrhage. Because of these hematologic findings, the infant was tested for a TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and other organisms including syphilis, parvovirus, and varicella zoster) infection, and found to have congenital cytomegalovirus infection. This was confirmed with DNA and RNA polymerase chain reaction. As a result of this infection, the mother and father were tested for HIV and found to be positive.*

A high index of suspicion is needed to diagnose HIV in areas with an increased incidence. This case also highlights the fact that women may test negative early in pregnancy but become infected at a later time during the pregnancy. Unfortunately, risk factors for HIV-positive status are not always apparent. Many such cases have been reported of recent conversion in high-incidence areas, primarily in teens and young adults. This has led to recommendations for HIV testing for women in these areas not only in the first trimester, but also late in the third trimester or during labor and delivery. (12) A positive HIV result during late pregnancy or labor and delivery offers the opportunity to provide HIV prophylaxis to the infant. In such high-risk cases, prophylaxis with zidovudine is often extended to 6 weeks rather than the current standard 4-week period, and a second drug, nevirapine, is added to the regimen. This combination has been shown to decrease the chances of MTCT of HIV. (10)

Recommendations to limit the incidence of perinatal HIV have been revised and updated throughout the years. HIV testing has long been recommended as standard of care for all sexually active women before conception and it should be a component of routine health care. If the HIV test result is negative, women should be tested as soon as they know they are pregnant. For many years, it was considered adequate that HIV-negative women should be tested in the third trimester only if they were considered high risk for HIV. High risk was defined as women who were diagnosed with another sexually transmitted infection, intravenous drug users, commercial sex workers, incarcerated, and resided in areas with an HIV incidence in pregnant women of at least 1 per 1,000. However, risk factors are not always apparent, and clinicians do not always reliably identify

women at risk for HIV; in fact, women do not always know they are at risk. Because of missed cases, some states in the United States have changed recommendations or laws to encourage broad third-trimester testing. Universal third trimester or at delivery testing is the most reliable way to ensure that almost all HIV-positive cases are identified.

If a pregnant woman is in labor and her HIV status is unknown, rapid HIV testing is ideal. If the result is positive, intrapartum and postnatal antiretroviral drug prophylaxis should be initiated immediately, while waiting for the results of supplemental HIV testing. If a pregnant woman has not been tested for HIV before or during labor, she should be tested in the immediate postpartum period. If the mother's HIV test result is positive, an appropriate antiretroviral drug regimen should be initiated immediately for the infant and the mother should not breastfeed unless the result of supplemental HIV testing is negative.

### Case Two

*Patient 2 was 21 years old when her son was born. She had been diagnosed with perinatal HIV in the early 1990s when she was only 8 years old. Her father died in prison of HIV-related complications, and her mother lost custody secondary to failure to provide her medications. The patient was raised by her maternal aunt, but never took HIV medication regularly. Stated reasons were difficulty swallowing pills, bad taste of the liquid medication, and finally being "tired" of the medication. She had been in many adherence programs growing up, and even had been admitted for directly observed therapy to ensure that she was not resistant to therapy. She had developed resistance to several HIV medications, but when observed, her HIV viral load did respond to the prescribed therapy and decreased to undetectable levels. When she returned home and underwent a home intervention of multisystemic adherence therapy, she responded for about 6 months, then stopped her medications again. She underwent motivational interviewing-based therapy as a teen and responded for about 6 months, then relapsed to nonadherence. She did not take medication during her pregnancy and her son was positive on his first HIV DNA. Her son's HIV prophylaxis therapy was stopped and he began receiving ART. He was subsequently found to have an inherited resistant virus, but has been maintained on a salvage regimen. Patient 2 died of an HIV-related illness when her son was 3 years old. He is being raised by the same maternal aunt who raised his mother.*

Poor adherence to ART results in some cases of perinatal HIV. A well-recognized group of teens and adults with poor ART adherence are those with perinatal HIV who have been taking medications on and off, received maintenance sequential monotherapies early in life, and were subjected to many early therapies with severe side effects and poor

tolerability. These patients developed multiple aversions and resistant virus, and were often poorly supervised by ill or overstressed caregivers. (13)(14) Patient 2's poor adherence during pregnancy led to perinatal infection in her son. Breaking the cycle of poor adherence with the introduction of treatments that are easier to administer and more palatable will help break this cycle for more recent perinatal patients when they reach child-bearing age. In addition, improved adherence strategies, including in-home adherence therapy, may be essential for the current generation of perinatal patients reaching childbearing age.

### Case Three

*Patient 3 was diagnosed with HIV at 18 years of age when she presented to the emergency department with pneumonia. She was referred to an adolescent clinic, but was unwilling to take medication. She frequently questioned the validity of her positive testing, and was lost to follow-up in less than a year. She became pregnant at 22 years of age and went to another medical center for care, hoping they would not be aware of her HIV status. Her obstetrician offered routine first-trimester HIV testing, and she was told she was positive but did not return for care until she was in labor. She was given intravenous zidovudine, and the infant was started on zidovudine treatment. The infant's first 2 HIV DNA test results were negative. The third test at 4 months, however, was positive. Patient 3 later reported that she had breastfed her infant. Since her infant's results, she has accepted her own diagnosis and started ART. She has also consistently provided her infant with ART.*

Although recent studies have shown that an undetectable HIV viral load signifies that the virus is not transmittable by sexual contact, (15) it is not clear if this is also true for breastfeeding. At this time, US clinicians still advise all HIV-positive mothers to avoid breastfeeding. Breastfeeding with an elevated HIV viral load is absolutely a risk factor for MTCT. (16) Patient 3 did not acknowledge her HIV-positive status and was not taking ART during her pregnancy. Another concern with breastfeeding is shared breastmilk. In the authors' practice, an HIV-positive mother did not learn of her diagnosis until her infant was diagnosed with HIV at 6 months of age. She had been breastfeeding and storing breastmilk to sell. After her HIV status was known to be positive, the health department assisted her with removal of her stored milk and notified those who had received her milk.

### SUMMARY

Great progress has been made toward eliminating perinatal HIV; however, a small but consistent number of cases are still seen each year. Elimination of the stigma associated

with testing will help us reach the ultimate goal of complete prevention of perinatal HIV, as will improvement of adherence therapy for high-risk groups.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of maternal HIV infection and its management.
- Know the strategies employed to decrease fetal and neonatal HIV infection.
- Recognize infectious agents that are transmitted in human milk.

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1. The risk of perinatal human immunodeficiency virus (HIV) transmission has decreased to less than 1% in resource-rich areas because of routine HIV testing in pregnancy, multidrug antiretroviral therapy (ART), and a better understanding of the relationship between viral load and viral transmission. Which of the following statements regarding perinatal HIV transmission in the United States is CORRECT?
  - A. The number of perinatal HIV cases has remained stable since 2013.
  - B. There are approximately 200 new cases of perinatal HIV every year in the United States.
  - C. In the majority of perinatal HIV cases, a diagnosis of HIV is made in the mother before pregnancy.
  - D. About 70% of HIV-positive women receive prenatal care and ART during pregnancy.
  - E. Approximately 40% of perinatal HIV cases are born to black women.
2. HIV testing is recommended for all pregnant women. Which of the following recommendations to decrease mother-to-child-transmission is INCORRECT?
  - A. The initiation of ART as soon as the diagnosis is made is recommended.
  - B. The same ART regimens used in the general population can also be used in pregnant women.
  - C. Delivery via cesarean delivery is recommended for all women with a viral load of more than 1,000 copies/mL.
  - D. Administration of zidovudine intravenously at the time of cesarean delivery is recommended for women with high viral loads.
  - E. Virologic testing in all infants with perinatal HIV exposure should begin before 24 hours after birth.
3. A 39-week-gestational age infant was delivered to a mother with HIV who is receiving adequate ART throughout her pregnancy and with an undetectable viral load at the time of delivery. Which of the following statements regarding the management of this infant is CORRECT?
  - A. Virologic testing starting on day 1 after birth and initiation of ART for a total duration of 6 week.
  - B. Virologic testing starting on day 14 after birth and no ART.
  - C. Virologic testing starting on day 14 after birth and initiation of ART for a total duration of 4 weeks.
  - D. Virologic testing starting on day 1 after birth and initiation of ART for a total duration of 4 weeks.
  - E. Virologic testing starting on day 1 after birth and no ART.
4. An infant is considered to be at high risk for perinatal HIV transmission if the mother did not have prenatal care, did not receive adequate ART therapy, or did not achieve viral suppression. Which of the following treatment regimens is recommended for these high-risk infants?
  - A. Zidovudine for 4 weeks.
  - B. Zidovudine for 6 weeks.
  - C. Zidovudine for 4 weeks as well as nevirapine for 3 doses.
  - D. Zidovudine for 6 weeks as well as nevirapine for 3 doses.
  - E. Zidovudine for 6 weeks as well as nevirapine for 4 doses.

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5. Despite the progress made in preventing the perinatal transmission of HIV, there are still cases of perinatal HIV every year, even in the United States. Investigating the cause of current perinatal HIV cases has highlighted several opportunities for improvement. Which of the following statements regarding perinatal HIV transmission and opportunities to decrease transmission further is INCORRECT?
- A. Testing during the third trimester of gestation is not recommended in women with no risk factors.
  - B. Women living in an area with high HIV incidence of at least 1 per 1,000 should be tested twice during pregnancy.
  - C. For infants born to a mother who converted during pregnancy, a 6-week course of zidovudine and nevirapine is recommended.
  - D. Women with undetectable viral load cannot breastfeed.
  - E. Poor adherence to ART is a recognized risk factor for perinatal HIV transmission.

## Perinatal HIV Transmission: Missed Opportunities and Proposed Solutions

Hadeel Shihan, Samantha Arsenault and Elizabeth Secord

*NeoReviews* 2019;20:e79

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# Index of Suspicion in the Nursery

## 1 An Infant with Arm Swelling and Nodules

Leeann R. Pavlek, MD,\* Erica Braswell, MD\*

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### PRESENTATION

A male neonate is born via spontaneous vaginal delivery to a 28-year-old primiparous woman at 39 2/7 weeks of gestation after an uncomplicated pregnancy. Labor is complicated by prolonged fetal heart rate decelerations, but the mother declines a cesarean section and vacuum extraction is initially unsuccessful. At birth the neonate is apneic but maintains a heart rate greater than 100 beats/min throughout the resuscitation. He requires intubation for persistent apnea 4 minutes after birth. His Apgar scores are 2, 3, 5, and 5 at 1, 5, 10, and 20 minutes, respectively. His physical examination on admission to the NICU is significant for diffuse hypotonia, lethargy, and absence of primitive reflexes. His arterial blood gas measurement 1.5 hours after birth shows a pH of 7.32,  $P_{CO_2}$  of 32 mm Hg, and base deficit of 9. A blood culture specimen is collected and he starts empiric treatment with ampicillin and gentamicin.

The infant is transferred to a tertiary care NICU for therapeutic hypothermia and has moderate encephalopathy on admission. He has a fluctuant, boggy mass over his occipital skull and undergoes noncontrast head computed tomography, which shows a large subgaleal hemorrhage, skull fracture, and small ventricles concerning for cerebral edema. A significant drop in his hematocrit is noted, and he receives transfusions of packed red blood cells and fresh frozen plasma. He requires a dopamine infusion and stress-dose hydrocortisone to maintain age-appropriate blood pressures.

Electroencephalography (EEG) shows electrographic and clinical seizure activity, which is treated with phenobarbital and levetiracetam. He also receives a midazolam infusion for agitation while cooling.

He undergoes rewarming after 72 hours of therapeutic hypothermia. He is gradually weaned to room air and has no further seizures. He remains in the NICU while working on oral feeding skills. One month after admission, he is noted to have swelling of his left hand and forearm. Physical examination shows a scab on the back of the left hand, soft tissue swelling of the forearm, and palpable nodules along the metacarpals, wrist, and ulnar side of the forearm. Radiography shows extensive vascular calcifications and faint nodular calcifications of the dorsum of the wrist and hand (Fig 1). Magnetic resonance imaging demonstrates wall thickening and surrounding enhancement of the cutaneous venous structures. This shows enhancement of the subcutaneous soft tissues, myositis, and solid nodules with inflammatory changes over the dorsal hand and wrist (Fig 2).

### DISCUSSION

#### Diagnosis

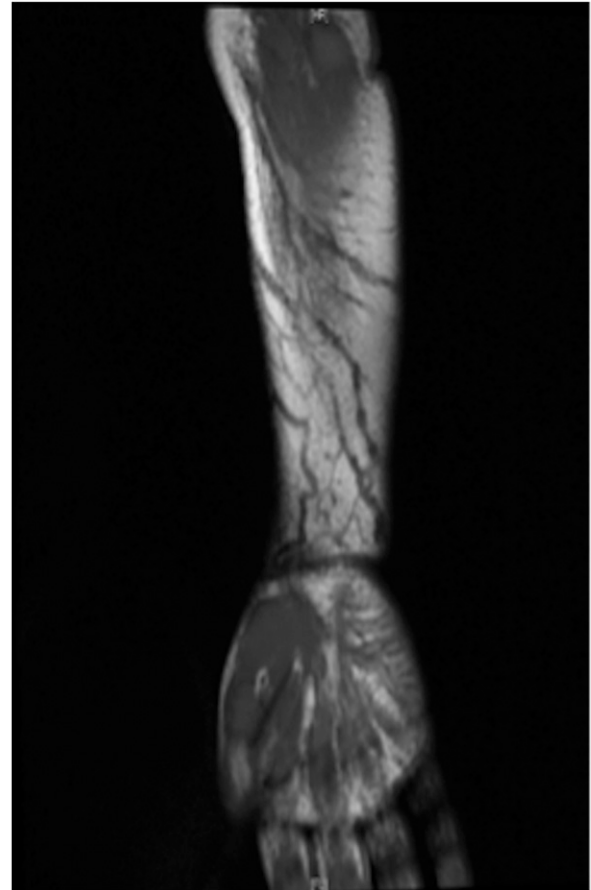
Based on the imaging findings, the differential diagnosis includes skin and vascular calcification due to calcium gluconate infusion, subcutaneous fat

**AUTHOR DISCLOSURE** Drs Pavlek and Braswell have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



**Figure 1.** A left arm radiograph demonstrates extensive vascular calcifications and nodular calcifications over the wrist and hand.

necrosis, or hypercalcemia. This presentation is consistent with calcinosis cutis, which is a condition in which insoluble calcium phosphate salts are deposited in the skin and subcutaneous soft tissue. (1) To evaluate for further vascular involvement, radiographs of the chest, abdomen, and right upper extremity are obtained and are normal. The serum calcium concentration on the day of the imaging is only mildly elevated at 10.7 mg/dL (2.7 mmol/L). Review of the medical record reveals that the infant received a dose of calcium gluconate via peripheral intravenous administration in the left hand during therapeutic hypothermia. Other medications



**Figure 2.** Magnetic resonance imaging scan of the left arm shows phlebitis, myositis, enhancement of the subcutaneous soft tissues, and solid nodules with inflammatory changes over the wrist and hand.

administered intravenously via the left hand included 10% dextrose in water, 0.9% sodium chloride, dopamine, gentamicin, ampicillin, phenobarbital, midazolam, and levetiracetam.

### The Condition

Several mechanisms for the development of calcinosis cutis have been suggested, including:

- An increase in cell membrane permeability resulting from local tissue injury, allowing an influx of calcium into the cytosol. The capacity for mitochondria to sequester calcium and phosphorus is exceeded, causing precipitation of calcium phosphate in the cytosol.
- Local tissue damage causing release of alkaline phosphatase, which increases the tissue pH and facilitates calcium phosphate salt precipitation.



- Fat cell necrosis because of local tissue damage leading to release of free fatty acids, which bind with calcium ions and form calcium soaps.

Local tissue injury often results from extravasation of intravenous medications, phlebitis, and repeated attempts to insert an intravenous line. (2)

This condition is divided into 5 subtypes, based on the underlying etiology:

- Dystrophic: Due to local tissue damage, with normal serum calcium and phosphorus levels.
- Metastatic: Due to abnormal calcium or phosphate metabolism, which causes calcium salts to precipitate in otherwise normal soft tissues.
- Iatrogenic: Calcium deposition into the skin as an adverse effect of medical therapy.
- Calciphylaxis: Calcification of small and medium arteries in the dermis and subcutaneous tissues, often in the setting of end-stage renal disease or malignancy.
- Idiopathic: Calcium deposition without any underlying metabolic abnormalities or tissue damage. (3)

Previous case studies have described calcification of the hepatic vein in the setting of calcium gluconate administration via umbilical vein catheter (UVC), improper positioning of the UVC, and use for more than 7 days. (4) Many case reports include patients with iatrogenic calcinosis cutis after extravasation of a calcium gluconate or calcium chloride infusion. (5) Iatrogenic calcinosis cutis has also been reported on the heels of infants who had multiple heel sticks for laboratory collection and at the sites of EEG lead placement. (1)(6)

Dystrophic calcinosis cutis can rarely be seen in the NICU at the sites of subcutaneous fat necrosis after therapeutic hypothermia or in the setting of an intrauterine herpes simplex virus infection. (7) Metabolic calcinosis cutis can be seen in neonates with rhabdomyolysis, renal failure, and pseudohypoparathyroidism. (2) No other cases of peripheral vein calcification in the setting of calcium gluconate administration are reported in the literature.

### Treatment

Most cases of calcinosis cutis are expected to resolve within 8 weeks. (3) Heel stick calcinosis cutis has been reported to self-resolve in 18 to 30 months, though persistent, painful, or ulcerating lesions can be surgically excised. (6) In complicated cases of calcium extravasation involving a large area, skin grafting may be required. One case report even described compartment syndrome requiring fasciotomy as a complication of a calcium gluconate extravasation. (5) Management of the



Figure 3. A follow-up left arm radiograph 6 weeks after diagnosis shows complete resolution of the vascular calcifications.

underlying disease is needed for patients with metabolic calcinosis cutis in the setting of hypercalcemia or hyperphosphatemia. (8)

The current patient did not receive any treatment for his calcinosis cutis. Follow-up radiography performed 6 weeks after the initial diagnosis demonstrated complete resolution of the calcifications (Fig 3).

### Lessons for the Clinician

- Peripheral administration of calcium-containing fluids has the risk of extravasation and tissue injury, leading to calcinosis cutis.
- Hepatic and portal vein calcification can be seen in patients receiving calcium-containing fluids via the umbilical vein catheter.

- Calcinosis cutis can be a complication of multiple heel sticks or intravenous catheter placement attempts in the NICU.
- Calcinosis cutis is typically a self-limited condition in neonates and rarely requires treatment in neonates.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the causes and clinical manifestations of catheter complications of parenteral nutrition.
- Recognize the causes and clinical manifestations of metabolic complications of parenteral nutrition.
- Recognize the potential toxicities associated with the use of parenteral nutrition.
- Know the etiology and clinical manifestations of neonatal hypercalcemia.

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## Case 1: An Infant with Arm Swelling and Nodules

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# Index of Suspicion in the Nursery

## 2 Severe Hyperammonemia in a Neonate: An Alternate Ending

Sarah Sheppard, MD, PhD,\*† Heidi Herrick, MD,\*†  
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### PRESENTATION

A male infant is born at 38 weeks 3 days of gestational age to a gravida 5, para 1 woman via spontaneous vaginal delivery, after a pregnancy complicated by maternal preeclampsia. Maternal history is significant for 2 early miscarriages and an ectopic pregnancy. All prenatal laboratory findings, including maternal immunoglobulin G for herpes simplex virus (HSV), had been normal or negative. The family history is unremarkable. The infant requires normal newborn care and is discharged from the hospital on day 2 after birth. His parents note that he had been sleepy and a poor feeder. He is hypothermic and tachypneic at his first newborn visit to the pediatrician and is immediately referred to the emergency department.

Septic evaluation reveals HSV in both serum and cerebrospinal fluid. Ammonia concentration is normal and his complete blood cell count reveals leukopenia. Initial treatment includes acyclovir, cefotaxime, and ampicillin, narrowed within 48 hours to acyclovir monotherapy. His condition rapidly declines and he develops respiratory failure on hospital day (HOD) 1. The ammonia concentration is within the normal range (39  $\mu\text{g/dL}$  [28  $\mu\text{mol/L}$ ]). Feeding is initiated on HOD 2 with a subsequent rise in the ammonia concentration (113  $\mu\text{g/dL}$  [81  $\mu\text{mol/L}$ ]). Despite the cessation of feeding and initiation of moderate glucose infusion rate, the ammonia concentration rises to 538  $\mu\text{g/dL}$  (384  $\mu\text{mol/L}$ ) by HOD 4. The patient is transferred to a different hospital for metabolic consultation.

### DISCUSSION

Increased glucose infusion rate along with a bolus of sodium benzoate and sodium phenylacetate did not sufficiently improve this infant's hyperammonemia. Continuous renal replacement therapy (CRRT) was initiated when the ammonia concentration exceeded 700  $\mu\text{g/dL}$  (500  $\mu\text{mol/L}$ ). The highest measured ammonia concentration was greater than 1,400  $\mu\text{g/dL}$  (1,000  $\mu\text{mol/L}$ ). The patient's hyperammonemia initially improved with CRRT but quickly rebounded after stopping therapy, requiring further CRRT. CRRT was gradually weaned, and protein supplementation was slowly introduced through total parenteral nutrition, and the patient had no additional issues with hyperammonemia.

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In this case, a history of poor feeding, sleepiness, hyperammonemia developing after feeding, hyperammonemia out of proportion with liver dysfunction, and the degree of elevated ammonia concentration raised suspicion for proximal urea cycle defects. Not all proximal urea cycle defects are included on US newborn screening, and can be missed. The ultimate resolution of the hyperammonemia, even after initiation of protein-based feeds, made these diagnoses unlikely. Initial liver function tests, coagulation studies, newborn screening, and abdominal ultrasonography were normal. The patient had no lacticemia, hypoglycemia, ketonuria, or acidosis. Initial acylcarnitine profile, plasma amino acids, urine orotic acid, and urine organic acids, all measured before the infusion of sodium benzoate and sodium phenylacetate, resulted in no diagnostic pattern. Given the severity of the child's condition, rapid whole exome sequencing was performed and was also negative. Ultimately, the hyperammonemia was attributed to disseminated HSV infection, including severe HSV pneumonitis, similar to a previously reported case. (1)

This infant's hospital course was complicated by severe respiratory failure and acute respiratory distress syndrome necessitating high-frequency oscillator ventilation. He also suffered bilateral pneumothoraces requiring the placement of multiple chest tubes. Due to refractory air leak, despite maximal medical management including chest tubes, paralysis, and high frequency jet ventilation, the patient was placed on venoarterial extracorporeal membrane oxygenation (ECMO). Pneumothoraces resolved, and after 13 days, the patient underwent successful decannulation. He was weaned off respiratory support, and transitioned from parenteral to enteral nutrition. After ECMO, magnetic resonance imaging showed normal brain parenchyma with a small focus of extra-axial blood products over the left frontal lobe. The infant was discharged from the hospital. On follow-up at 9 months of age, the infant was feeding orally and growing well. ECMO was not available for the previously reported case, which was fatal. (1)

Ammonia is a byproduct of protein metabolism that, when elevated, can present with signs and symptoms of neurotoxicity. In a neonate, these include poor feeding, vomiting, lethargy, seizures, and encephalopathy and can mimic sepsis. (2)(3) Hyperammonemia may be precipitated by illness, such as sepsis, prematurity, liver immaturity, or inborn error of metabolism. Inborn errors of metabolism include primary urea cycle defect or secondary hyperammonemia in organic acidurias, mitochondrial disease, or substrate deficiencies. (2) Hyperammonemia is diagnosed

using a free-flowing blood sample placed on ice. (4) The underlying cause for the hyperammonemia should be determined simultaneously with treatments aimed at lowering the ammonia level in the patient. Laboratory evaluation should include plasma glucose, complete metabolic panel, coagulation factors, plasma acylcarnitines, plasma amino acids, urine organic acids, and urine orotic acid. (4) An evaluation for infection and liver imaging may also be clinically indicated.

Regardless of the origin, prompt management of hyperammonemia in the newborn is important for neurodevelopmental outcomes. (5)(6) Early in a disease process, the different etiologic factors may be indistinguishable. (2) Initial medical management includes decreasing ammonia production and increasing ammonia removal. (4) Preventing catabolism with high-dextrose intravenous fluids with a target glucose infusion rate of 8 to 10 mg/kg per minute and limiting protein intake may help to decrease the production of ammonia. Protein intake should be restricted for more than 24 to 48 hours because excessive protein restriction may lead to catabolism of endogenous protein. Nitrogen scavengers, such as sodium phenylbutyrate and sodium benzoate, will aid in the removal of ammonia. Amino acid supplementation may be helpful in primary urea cycle defects. The usefulness of dialysis in the treatment of hyperammonemia has been studied in patients with inborn errors of metabolism and sepsis. (1)(6)(7)(8) Indications for dialysis include blood ammonia levels of 560 to 700  $\mu\text{g/dL}$  (400–500  $\mu\text{mol/L}$ ) in neonates and insufficient response to medical management, though others have used thresholds of 280  $\mu\text{g/dL}$  (200  $\mu\text{mol/L}$ ). (4)(9) In the management of hyperammonemia, it is extremely important to be cognizant of one's resources, because timely transfer of the neonate to a metabolic center or larger children's hospital with access to ammonia scavengers and dialysis may be necessary. Early consultation with a metabolic physician is recommended.

### Lessons for the Clinician

- Always consider hyperammonemia in the evaluation for neonatal sepsis, especially in the setting of poor feeding, vomiting, lethargy, seizures, and encephalopathy.
- Early management of hyperammonemia is crucial for improved neurodevelopmental outcomes and transfer to a metabolic center or larger children's hospital may be necessary.
- Lung rest strategies via extracorporeal membrane oxygenation are a potential solution for refractory air leak in a neonate.



## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.
- Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants.
- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.

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# Index of Suspicion in the Nursery

## 3 The Hypothermic Newborn

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### PRESENTATION

A 2-day-old male infant born at 38 weeks to a gravida 1, para 1 woman is brought to the emergency department secondary to concerns for hypothermia, poor feeding, and decreased urine output. Prenatal laboratory results are unremarkable, with the exception of group B *Streptococcus* colonization that was adequately treated with penicillin prophylaxis before delivery. The delivery course was notable for thick meconium for which the infant underwent intubation and suctioning with subsequent extubation. The infant's Apgar scores were 4 and 9 at 1 and 5 minutes, respectively. In the nursery, the infant was noted to be breastfeeding well and had passed stools and voided appropriately. He was discharged on day 2 after birth.

After discharge, the parents contacted the infant's physician to report decreased interest in feeding, decreased activity, and low rectal temperature of 93.9°F (34.4°C). The family was instructed to take the infant to the emergency department for further evaluation and treatment. On arrival at the emergency department, the infant was noted to have a temperature of 96.9°F (36.1°C) and to be listless, and was thus taken to a resuscitation bay. Initial physical examination showed an ill-appearing infant with tacky mucous membranes and an exaggerated Moro reflex. He was given a 10-mL/kg normal saline bolus and a 15-mL/kg normal saline bolus.

Initial laboratory findings include the following: white blood cells 22,000/ $\mu$ L ( $22 \times 10^9$ /L); hemoglobin 13.3 g/dL (133 g/L); hematocrit 36.5%; platelet count,  $565 \times 10^3$ / $\mu$ L ( $565 \times 10^9$ /L); neutrophils 80%; bands 1%; lymphocytes 12%; monocytes 5%; sodium 154 mEq/L (154 mmol/L); potassium 5.1 mEq/L (5.1 mmol/L); chloride 115 mEq/L (115 mmol/L); bicarbonate 20 mEq/L (20 mmol/L); blood urea nitrogen 6 mg/dL (2.14 mmol/L); creatinine 1.4 mg/dL (123.7  $\mu$ mol/L); and glucose 102 mg/dL (5.6 mmol/L). These tests were interpreted as leukocytosis with neutrophilic predominance but without a significant proportion of immature cells, hypernatremia, and an anion-gap metabolic acidosis. Cerebrospinal fluid (CSF) and urine specimens were collected and results were as follows: CSF white blood cells 7,000/ $\mu$ L ( $7 \times 10^9$ /L); CSF red blood cells  $149 \times 10^6$ / $\mu$ L ( $149 \times 10^{12}$ /L); CSF glucose 63 mg/dL (3.5 mmol/L); CSF protein 96 mg/dL (960 mg/L); urine pH 6.0; urine leukocyte esterase negative; urine nitrite negative; urine bacteria many; urine white blood cells negative. Neonatology was consulted at this point. Initiation of ampicillin and gentamicin and admission to the special care nursery were recommended.

The infant was subsequently transferred to the special care nursery where he was noted to have a distended abdomen; an anteroposterior abdominal radiograph showed intraluminal distention but no free air, pneumatosis coli, or

**AUTHOR DISCLOSURE** Drs Erickson and Schrier Vergano have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

portal venous gas. He subsequently became apneic and underwent intubation and was transferred to the NICU for further management. On arrival at the NICU, umbilical arterial and venous lines were placed, through which intravenous fluids were administered at a rate of 140 mL/kg per day and a Foley catheter was placed to monitor urine output. Given the elevated creatinine level, gentamicin was discontinued and cefotaxime was started. The infant was also started on oxacillin treatment at this point to broaden empiric coverage. A capillary blood gas, ammonia level, repeat hemoglobin/hematocrit, and coagulopathy panel measurements were obtained. The results of these tests were as follows: blood pH 7.07;  $P_{CO_2}$  71 mm Hg (9.5 kPa); base excess -9; ammonia more than 1,400  $\mu$ g/dL ( $>1,000 \mu$ mol/L), hemoglobin 9.9 g/dL (99 g/L); hematocrit 29%; prothrombin time 22.4 seconds; partial thromboplastin time 46.6 seconds; fibrinogen level 131.2 mg/dL (3.8  $\mu$ mol/L). These results were interpreted as a likely metabolic derangement with concomitant coagulopathy and respiratory acidosis. The infant was given 15 mL/kg of packed red blood cells and 10 mL/kg of fresh frozen plasma; ventilator settings were adjusted to increase ventilation; and medical genetics was consulted.

Based on genetics recommendations, the infant was started on the intravenous nitrogen scavenger sodium phenylacetate and sodium benzoate and arginine infusion. The infant continued to undergo serial ammonia and lactate measurements; additional metabolic laboratory studies were performed, including plasma amino acids, urine organic acids, acylcarnitine profile, and urine orotic acid. Despite the nitrogen scavenging medications, the infant continued to have ammonia levels greater than 1,358  $\mu$ g/dL (970  $\mu$ mol/L) for the remainder of the morning of admission. An internal jugular vein central venous line was placed in preparation for dialysis. After this, the infant's ammonia level began to show a downward trend to 393  $\mu$ g/dL (281  $\mu$ mol/L), continued to decrease to 93  $\mu$ g/dL (67  $\mu$ mol/L) in the following 24 hours, and normalized on the following day.

## DIAGNOSIS

Plasma amino acid and urine organic acid results were obtained within 48 hours, and were remarkable for increased citrulline, excretion of argininosuccinate anhydrides, and positive urine orotic acid. These results suggested a diagnosis of argininosuccinate (ASA) lyase deficiency. Low-protein total parenteral nutrition was started on hospital day 3 and nasogastric feeds were initiated on day 6 of hospitalization with a mixture of amino acid-restricted

formula and breast milk, given the presumptive diagnosis of ASA lyase deficiency. Genetic testing demonstrated that the infant was heterozygous for 2 pathogenic variants of the *ASL* gene, confirming the diagnosis. The infant's newborn screening performed at 11 days after birth showed an elevated citrulline level. The infant continued to improve and was taken off all support with excellent oral feeds. He was subsequently discharged from the hospital with a nasogastric tube in place for medications and to continue with arginine, sodium benzoate, and sodium phenylbutyrate. He continued to receive close follow-up by his pediatrician and medical genetics specialist and ultimately received an orthotopic liver transplant at 8 months of age. He continues to thrive and meet his developmental milestones.

## THE CONDITION

ASA lyase deficiency is an autosomal recessive condition with an estimated incidence of approximately 1 in 70,000 live births. (1) ASA lyase is the enzyme involved in the urea cycle, which breaks down ASA to produce fumarate and arginine. The deficiency or lack of this enzyme causes buildup of citrulline, the compound detected on newborn screening for identification of ASA lyase deficiency. Elevated citrulline can also be seen in citrullinemia, another urea cycle disorder, as well as pyruvate dehydrogenase deficiency. As such, plasma amino acids must be checked for levels of ASA and its anhydrides to confirm the diagnosis of ASA lyase deficiency. Infants with ASA lyase deficiency (or other urea cycle disorders) will typically present with feeding difficulties and hypothermia after an initial period of wellness. As ammonia levels climb, however, the infant will have increasing central nervous system signs because of cerebral edema, and may include respiratory alkalosis, lethargy, seizures, and coma. Unique to ASA lyase deficiency are the findings of systemic hypertension and trichorrhexis nodosa (areas of partial alopecia with brittle hair). (2)

It is typically treated in the acute phase with nitrogen scavenger therapy, arginine supplementation, and a protein-free diet while still providing adequate glucose to prevent catabolism. If the clinician is unable to normalize the serum ammonia levels, hemodialysis must be considered. Over the long term these patients do benefit from orthotopic liver transplantation because this will prevent further metabolic crises.

## Lessons for the Clinician

- Clinicians should have a high index of suspicion for hyperammonemia when infants present with hypothermia,

tachypnea, poor feeding, and lethargy between 2 and 7 days of age.

- Once the diagnosis of hyperammonemia is made, prompt therapy with arginine, nitrogen scavenger therapy, and prevention of catabolism, while restricting protein intake, is crucial to reduce the ammonia levels and potentially prevent the impact on neurocognition.
- An elevation of citrulline on newborn screening is suggestive of argininosuccinate lyase deficiency, citrullinemia, or pyruvate carboxylase deficiency. To clarify the diagnosis from this point, a serum amino acid panel is necessary.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.

- Recognize the clinical and laboratory manifestations of metabolic acidosis and metabolic alkalosis in infants.
- Know the causes and differential diagnosis of metabolic acidosis and metabolic alkalosis in infants.

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**Case 3: The Hypothermic Newborn**  
Joshua Erickson and Samantha A. Schrier Vergano  
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## Recognizing the Progression to Category III Tracing: Late Decelerations

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

**AUTHOR DISCLOSURE** Dr Demasio has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - o Normal: ≤5 contractions in 10 minutes
  - o Tachysystole: >5 contractions in 10 minutes

#### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

- Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
    - Bradycardia not accompanied by absent variability
    - Tachycardia
    - Minimal or marked baseline variability
    - Absent variability without recurrent decelerations
    - Absence of induced accelerations after fetal stimulation
    - Recurrent variable decelerations with minimal or moderate variability
    - Prolonged decelerations
    - Recurrent late decelerations with moderate variability
    - Variable decelerations with other characteristics, such as slow return to baseline
  - Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
    - Absent variability with any of the following:
      - Recurrent late decelerations
      - Recurrent variable decelerations
      - Bradycardia
    - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health

and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## THE CASE

A 25-year-old primigravida came to the labor and delivery (L&D) department complaining of vaginal bleeding that started earlier that evening, with uterine contractions that began soon after. She was 38 5/7 weeks of gestation by her last menstrual period, which was also consistent with a second-trimester ultrasound examination performed at 16 weeks of gestation. The prenatal course was unremarkable except that she began her prenatal care in the second trimester at 16 weeks of gestation. Her prenatal laboratory results were within normal limits, and result of a second-trimester quad marker screening test for aneuploidy was also negative. Fetal anatomical survey performed at approximately 22 weeks of gestation did not reveal any structural abnormalities. Her medical and surgical histories were otherwise noncontributory.

On initial examination in the L&D unit, she had a blood pressure of 144/76 mm Hg, heart rate of 73 beats/min, normal temperature, and a body mass index of 33 kg/m<sup>2</sup>.

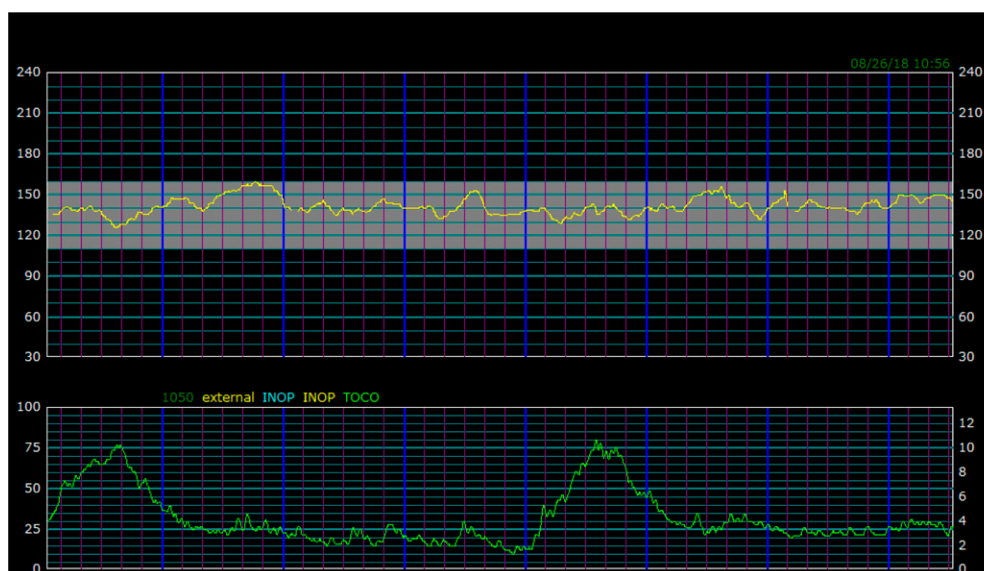


Figure 1. Electronic fetal monitoring strip 1.

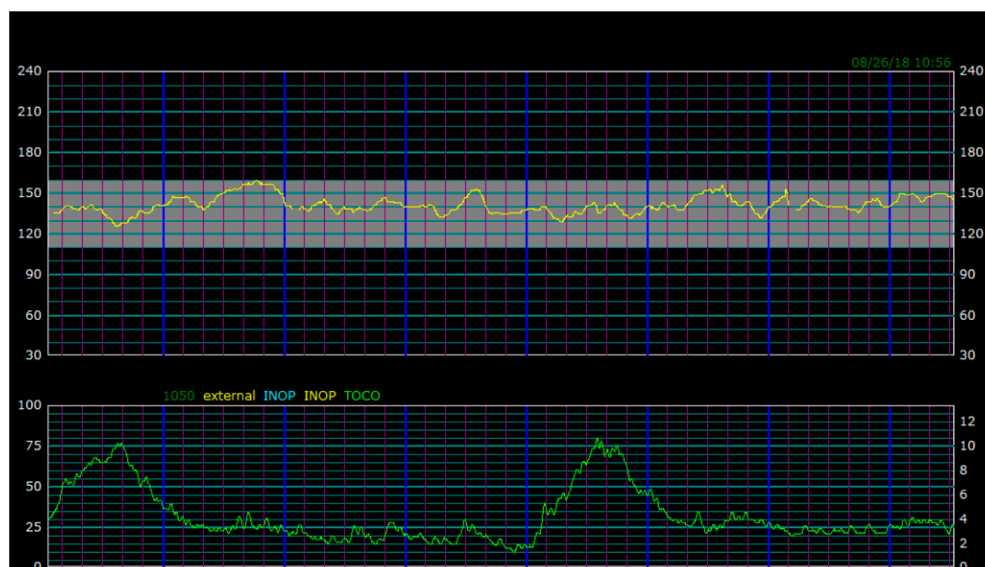


Figure 1. Electronic fetal monitoring strip 1.

The FHR tracing was a category I (Fig 1). The estimated fetal weight was assessed using Leopold maneuvers and was thought to be 3,200 g. The vaginal examination was 2 cm dilated, 90% effaced, and the station was “floating” at –5. On reexamination after 2 hours, she had the same cervical status. At this point in her evaluation, her laboratory studies revealed a platelet count of  $116 \times 10^3/\mu\text{L}$  ( $116 \times 10^9/\text{L}$ ) and a urine protein-creatinine ratio of 379.9 mg/g. In light of her elevated blood pressure and elevated spot urine protein, the

decision was made to admit her for monitoring and further management even though she was not in labor.

Four hours after her admission, she requested pain medication, which prompted a repeat pelvic examination. Her cervix had progressed to 3 cm dilation, 90% effacement, and –2 station, and her platelet count was now  $173 \times 10^3/\mu\text{L}$  ( $173 \times 10^9/\text{L}$ ), suggesting that the first result had been falsely decreased. At the request of the woman, epidural analgesia was provided by the anesthesiologist, and within 30 minutes



Figure 2. Electronic fetal monitoring strip 2.





Figure 2. Electronic fetal monitoring strip 2.

of epidural placement, a category II tracing was noted (Fig 2).

Intrauterine resuscitation was provided with maternal repositioning, oxygen by face mask, and an intravenous fluid

bolus. She was evaluated about 45 minutes later when her blood pressure was 138/101 mm Hg and heart rate was 66 beats/min; her cervical examination showed 5 cm dilation, 90% effacement, and -1 station. The FHR tracing was

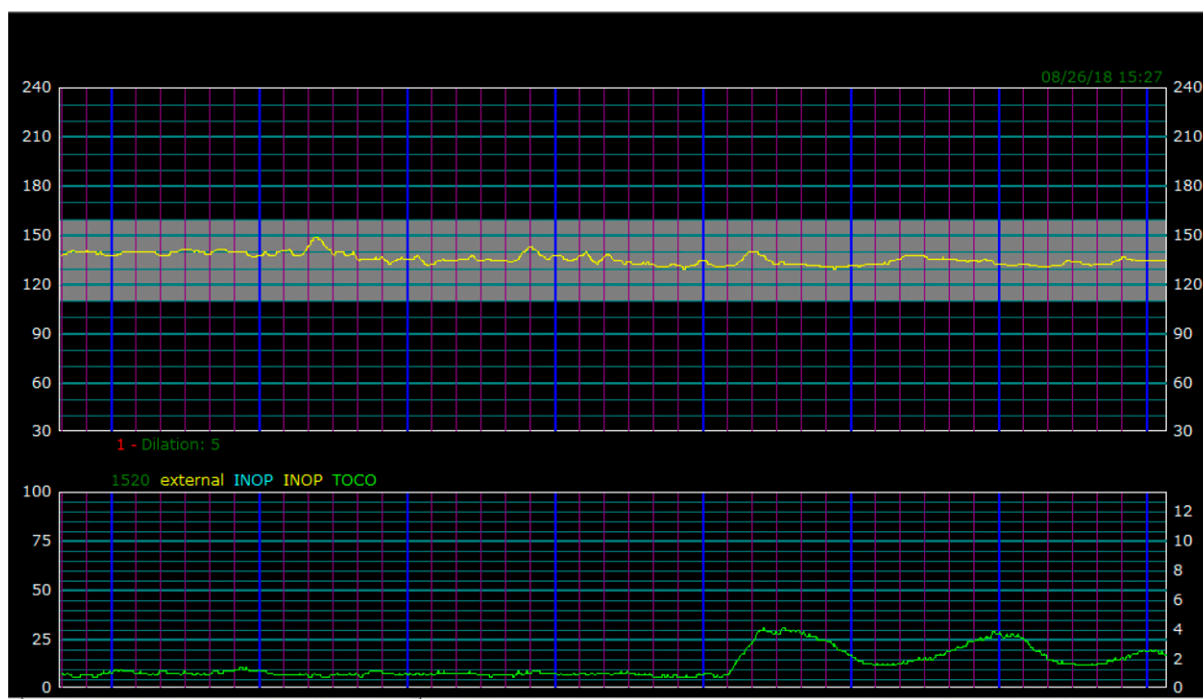


Figure 3. Electronic fetal monitoring strip 3.

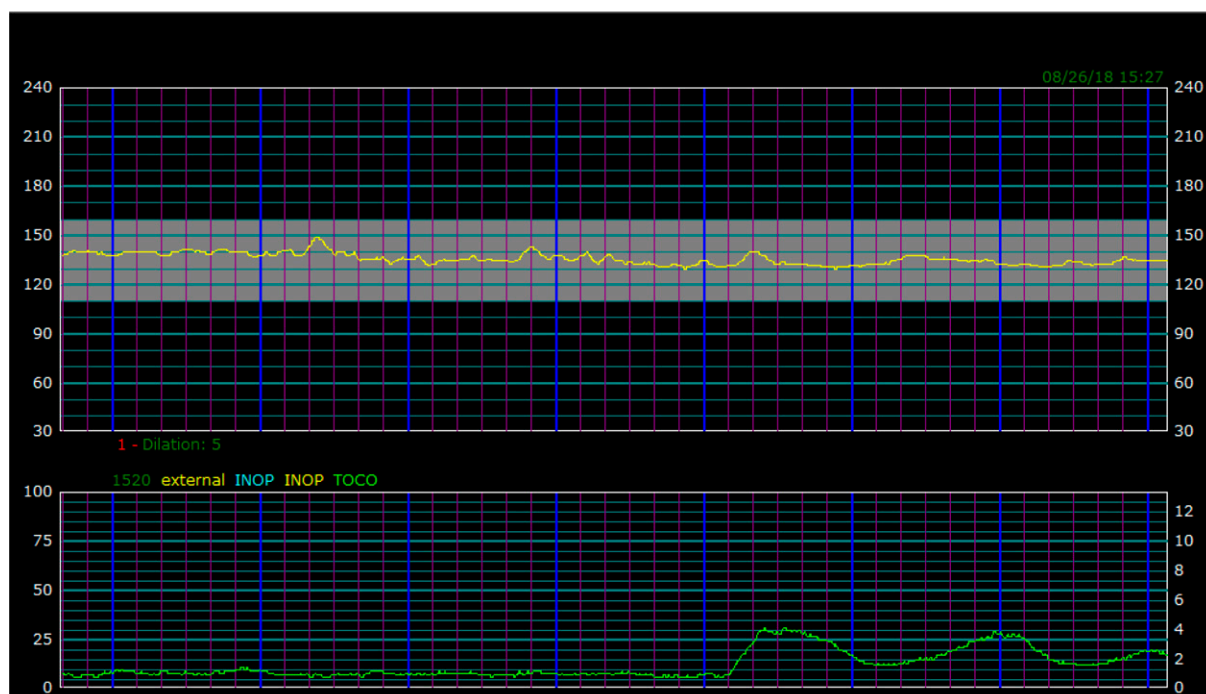


Figure 3. Electronic fetal monitoring strip 3.

category I (Fig 3), without accelerations or decelerations, so membranes were artificially ruptured to expedite labor. Meconium-stained amniotic fluid was noted and it was planned

to reexamine her cervix as clinically indicated. After approximately 2 hours, the FHR tracing became concerning because of minimal variability and recurrent late decelerations (Fig 4).

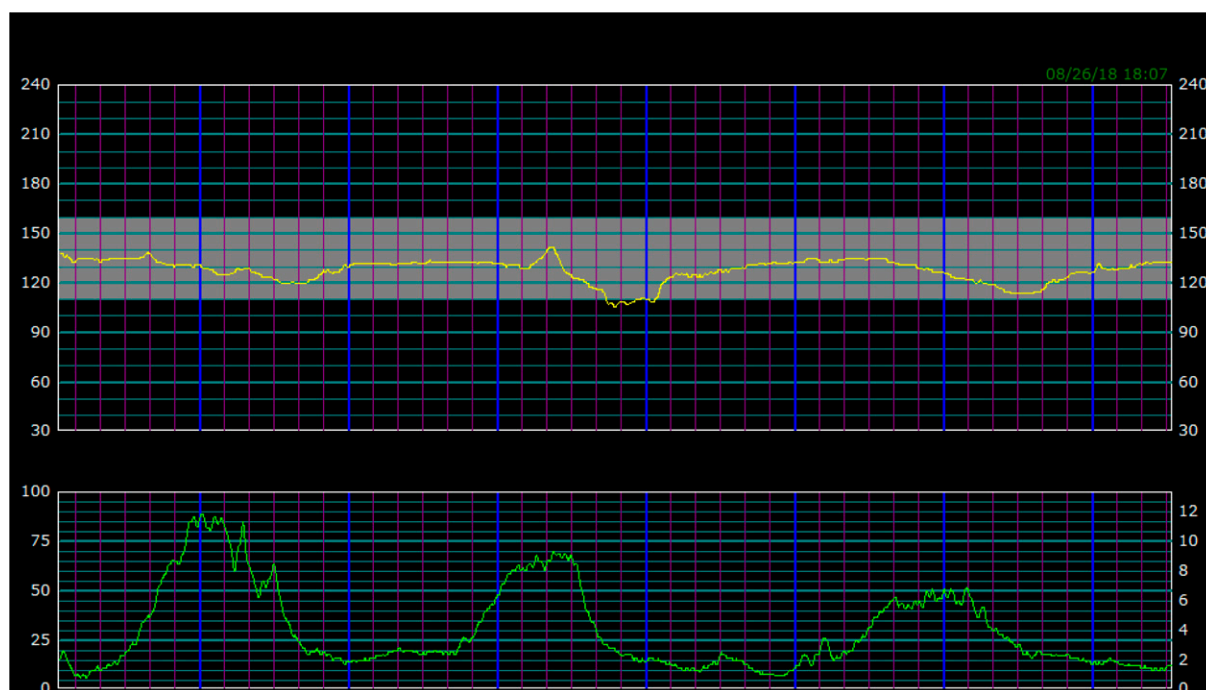


Figure 4. Electronic fetal monitoring strip 4.

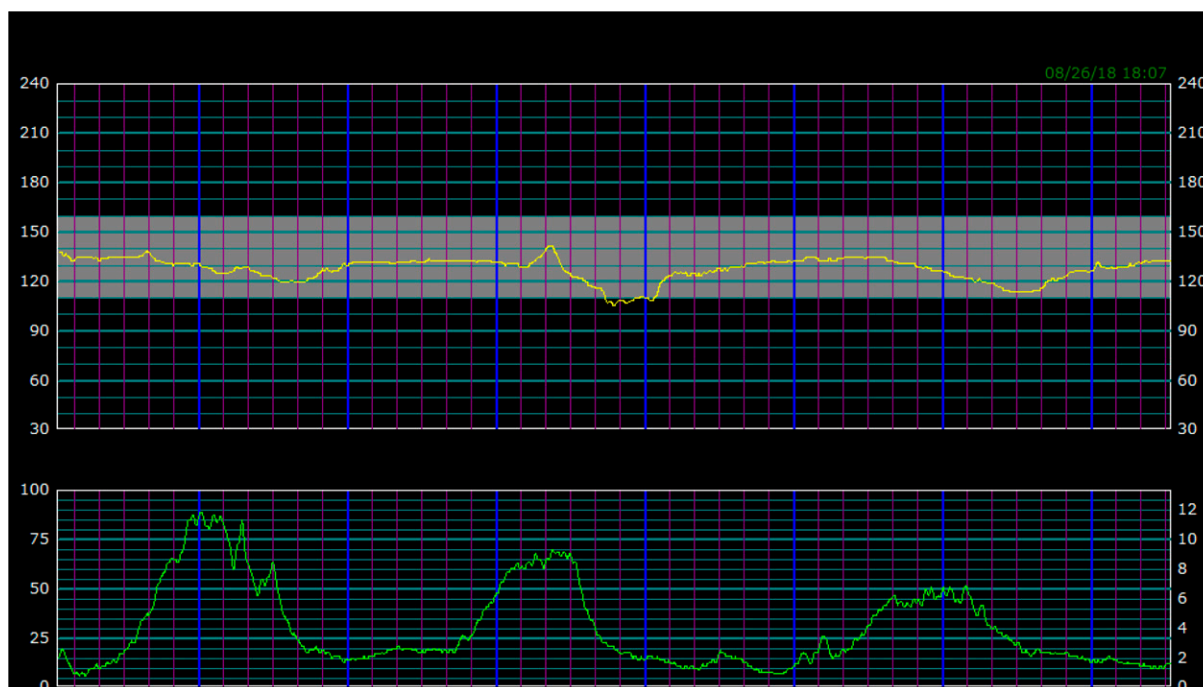


Figure 4. Electronic fetal monitoring strip 4.

The clinician noted that the FHR tracing had deteriorated and become a nonreassuring category II tracing. Cesarean delivery was recommended because the status of her cervix was unchanged from the prior examination 2 hours earlier. However, delivery was delayed because the

L&D department was busy, and the team's assessment was that the need for delivery was not emergent. The delivery was performed 1 hour later, and the FHR tracing in Fig 5 represents the FHR tracing in the last hour before delivery.

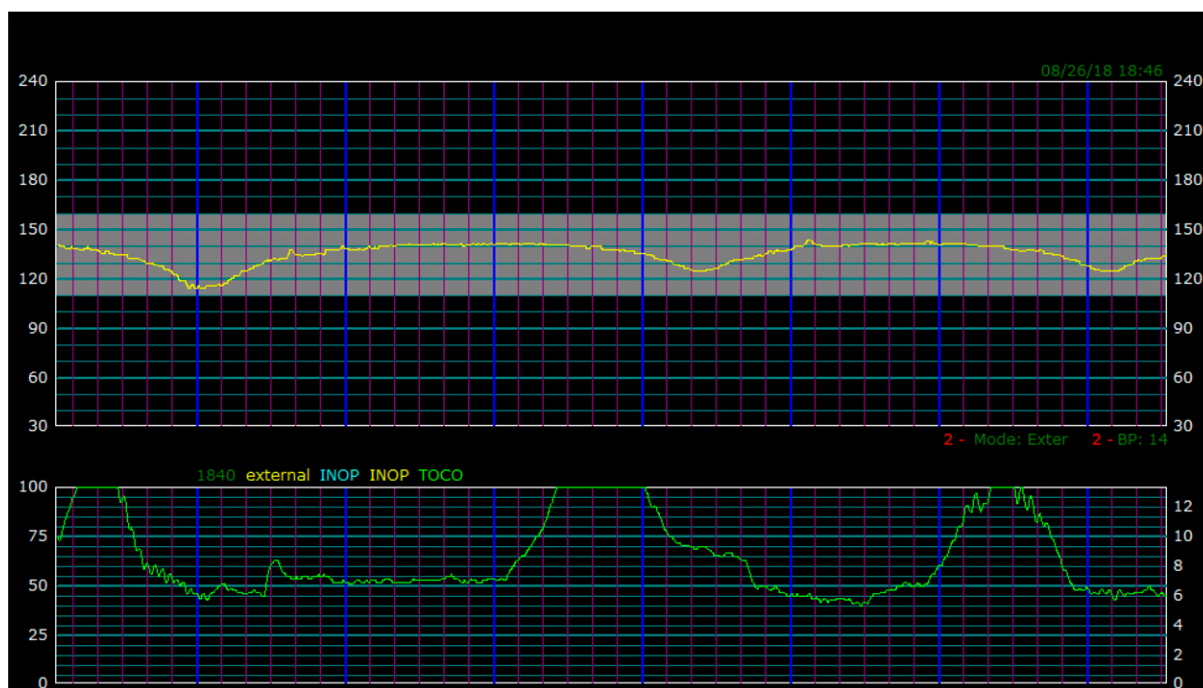


Figure 5. Electronic fetal monitoring strip 5.

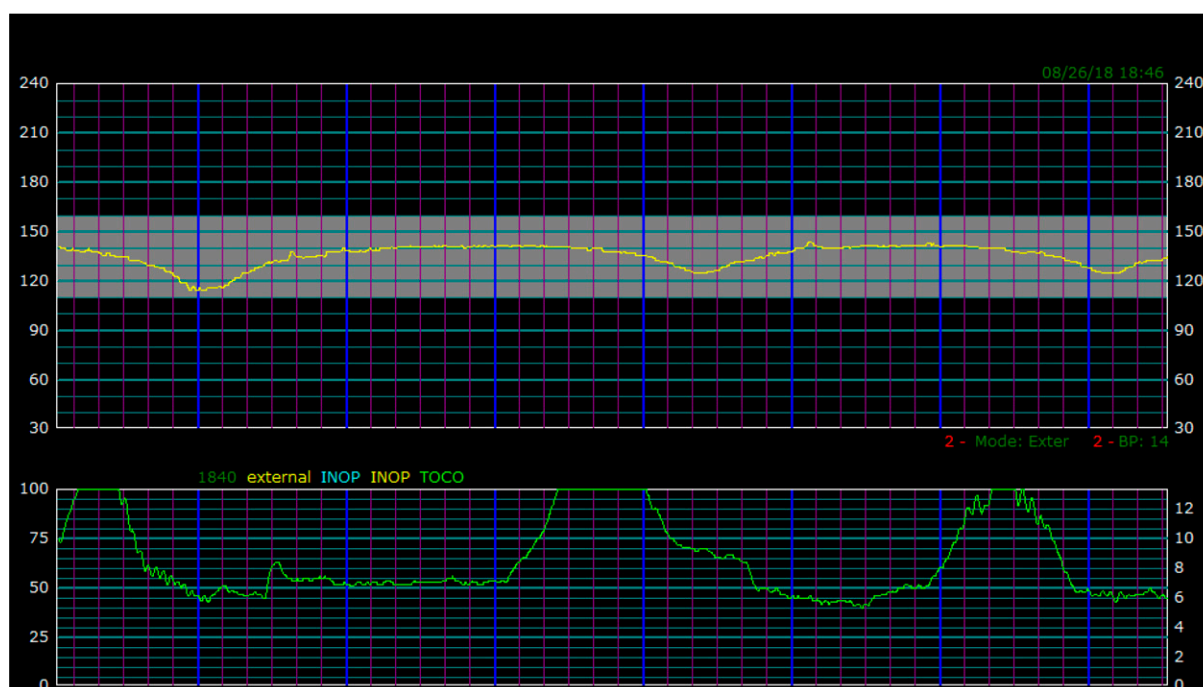


Figure 5. Electronic fetal monitoring strip 5.

A female infant was delivered from a cephalic presentation with a nuchal cord. The infant was assessed to be floppy and pale with no respiratory effort that prompted intubation. However, at 10 minutes of age, the infant's tone improved and the infant had spontaneous breathing and crying, prompting elective extubation and transition to continuous

positive airway pressure in the delivery room. The infant's Apgar scores were 1 and 6 at 1 and 5 minutes, respectively. The umbilical cord gases are shown in Table 2. The infant's birthweight was 2,680 g. After admission to the NICU for further observation, she was weaned to room air within a few hours. After ruling out infection and treating with a

TABLE 2. Umbilical Cord Gas Values for the Neonate

CORD GASES	PATIENT	REFERENCE RANGE
Arterial		
pH	6.90	7.35–7.45
Pco <sub>2</sub> , mm Hg (kPa)	113 (15)	35–45 (4.7–5.9)
Po <sub>2</sub> , mm Hg (kPa)	32 (4.2)	80–100 (11–13)
Base excess, mEq/L (mmol/L)	–10.9	10–2
Bicarbonate, mEq/L (mmol/L)	21	22–28
Venous		
pH	6.95	7.35–7.45
Pco <sub>2</sub> , mm Hg (kPa)	104 (13.8)	35–45 (4.7–5.9)
Po <sub>2</sub> , mm Hg (kPa)	10 (1.3)	80–100 (11–13)
Base excess, mEq/L (mmol/L)	–9.2	10–2
Bicarbonate, mEq/L (mmol/L)	22	22–28

short course of antibiotics, the infant was ultimately discharged from the NICU 5 days after birth.

## DISCUSSION

Most women with uncomplicated term pregnancies who are admitted to L&D with a category I FHR tracing, which then develops into a category II tracing, will deliver an infant without signs of acidosis or need for admission to the NICU, regardless of the mode of delivery. The FHR patterns in these cases are usually associated with moderate baseline variability, even in the absence of accelerations, and the presence of decelerations. However, delivery of a depressed term infant who requires more than basic neonatal resuscitation and subsequent admission to the NICU raises the concern for fetal acidosis because of poor fetal oxygenation during the stress of labor. The FHR pattern most associated with uteroplacental insufficiency, and therefore the risk of poor fetal oxygenation, is recurrent late decelerations, as demonstrated by this case (Figs 4 and 5).

Late decelerations are associated with both transient and chronic uteroplacental insufficiency. The FHR tracing in this case changed immediately after epidural analgesia was administered (Fig 2) but recovered. Maternal hypotension is a common transient cause of FHR abnormalities, which usually responds to intravenous fluid resuscitation. A randomized double-blind, double placebo-controlled trial with approximately 100 pregnant women in each arm compared 3 neuraxial techniques. The authors reported that the occurrence of hypotension was about 30% with all 3 techniques, and was not associated with nonreassuring FHR tracing. Rather, the use of intrathecal sufentanil induced FHR abnormalities during labor and the combined spinal epidural caused more severe hypotension and required higher doses of ephedrine treatment. (1) The initial recovery of the FHR tracing after an intravenous fluid bolus can be attributed to an increase in uteroplacental perfusion and maternal oxygenation. In cases in which labor is rapidly progressing, recovery of the FHR tracing may allow for a vaginal delivery. However, in the case described herein, the tracing developed into recurrent late decelerations without any progression in labor; the umbilical arterial cord gas values (Table 2) reflect a respiratory acidosis. Of note, this infant's umbilical venous gas (Table 2), which reflects the maternal oxygenation and uteroplacental delivery to the fetus, was also compromised.

The factors that decrease venous cord pH are maternal and placental factors.

Recurrent late decelerations are associated with both category II and category III FHR tracings, with the difference being the presence or absence of baseline variability, respectively. (2) Whereas the former may respond to intrauterine resuscitative measures and resolve, the latter requires expeditious delivery. Because the National Institute of Child Health and Development classification is based on the visual inspection of the FHR tracing, differentiating a category II from category III FHR tracing can vary based on the experience of the clinician. In one study, the interobserver variability among 3 maternal-fetal medicine subspecialists for category III FHR tracing segments was poor ( $\kappa=0.0$ ). (3) Although the clinician in the current case recognized the need for delivery because of the deteriorating fetal status and lack of labor progression, the late decelerations persisted and failed to respond any further to intrauterine resuscitative measures. The tracing progression to absent baseline variability became a category III FHR tracing warranting delivery as expeditiously as possible. The speed with which the delivery should be performed to prevent hypoxic-ischemic encephalopathy or improve neonatal outcome is not well-established. (2)

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know how to assess fetal well-being during labor.

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## Strip of the Month: Recognizing the Progression to Category III Tracing: Late Decelerations

Kafui Demasio

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**Strip of the Month: Recognizing the Progression to Category III Tracing: Late Decelerations**

Kafui Demasio

*NeoReviews* 2019;20:e96

DOI: 10.1542/neo.20-2-e96

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## Tachysystole, Uterine Rupture, and a Bad Outcome

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**AUTHOR DISCLOSURE** Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A 30-year-old gravida 3, para 1 woman presented at 41 weeks' gestation for induction of labor. The pregnancy had been unremarkable. Two years before this pregnancy, the woman had undergone a cesarean after protracted labor that resulted in the delivery of a term healthy infant. For this pregnancy, a decision to induce labor and have a trial of labor after cesarean was agreed upon by the woman and her obstetrician. Increasing amounts of oxytocin were administered. Nine hours after induction was started, her contractions dramatically increased in frequency. The intervals between the peak of contractions varied between 60 and 90 seconds and the time between the end of one contraction and the beginning of the next was less than 1 minute in most cases. Long periods of tachysystole emerged. *The obstetrician retained by the plaintiff stated that the treating obstetrician was required to decrease or discontinue the oxytocin when the contractions became too frequent. He explained that the time between the peak of one contraction and the next contraction needed to be at least 2 minutes and the interval between the end of one contraction and the beginning of the next needs to be at least 1 minute. He pointed out that these intervals were not maintained. He further explained that fetal gas exchange occurs during the rest phase between contractions and therefore, without proper rest intervals, gas exchange will eventually be compromised. He further pointed out that even the definition of tachysystole was met multiple times. He explained the definition of tachysystole was more than 5 contractions in a 10-minute period averaged over 30 minutes. He explained that excessive uterine activity was dangerous for the well-being of the fetus and stated that it should have been recognized as unacceptable. The obstetrician retained by the defense explained that the contractions did not produce excessive peak pressures and therefore, the frequent contractions were not a threat to the fetus. Also, the defense maintained that raising the oxytocin dose might be beneficial because sometimes it breaks through excessive uterine activity. The plaintiff disagreed with each assertion. He did agree that the contractions did not generate excessive peak pressures, but that the inadequate rest times were the problem in this situation, not the intrauterine pressure. The dose of oxytocin was irrelevant, because it was the response that the uterus had to oxytocin that was at issue. Also, he noted that to raise the dose of oxytocin in the face of excessive uterine activity was nonsense.*

By 11 hours after induction, heart rate accelerations disappeared, late and variable decelerations appeared, and variability became minimal to absent. Thirty minutes after these signs of fetal deterioration, the cervix was completely dilated and the woman had her first push. Immediately after the first push, despite an earlier epidural, the woman experienced severe abdominal pain and a drop in her heart rate. Severe variable decelerations began and these transitioned into fetal bradycardia, with heart rates ranging in the 80s. The nurse changed the woman's position, gave her oxygen and a fluid bolus, and

started terbutaline. No improvement was noted in the fetal status despite these interventions, prompting the nurse to call the obstetrician, who was at the bedside 25 minutes after the first push. Upon arrival, he learned that the nurse had tried various maneuvers (eg, lateral position) without success. He repeated these maneuvers, performed a vaginal examination, and placed a fetal scalp electrode. *The plaintiff obstetrician explained that he wasted time repeating the maneuvers and placing a scalp electrode; instead, he should have done a quick vaginal examination to determine if he could deliver the distressed fetus; within a minute, he could have determined that he could not promptly do a vaginal delivery and then he could have called for an immediate cesarean section, with anesthesiology alerted immediately as well.* At this point in the labor and delivery room, he discussed the need for an emergency cesarean section, had the papers signed, and then called for an immediate cesarean section. After the woman was brought to the operating room, anesthesiology was called and a cesarean section was performed within 30 minutes of the obstetrician calling for the cesarean section and 60 minutes after the first push that had led to the subsequent fetal deterioration. A lifeless fetus was found floating in the abdomen secondary to a uterine rupture.

The cord arterial gas had a pH less than 6.8, a  $P_{CO_2}$  of 133 mm Hg (17.7 kPa), a  $P_{O_2}$  of 8 mm Hg (1 kPa), and a base deficit that could not be calculated. The venous gas had a pH less than 6.8, a  $P_{CO_2}$  of 141 mm Hg (18.7 kPa), a  $P_{O_2}$  of 10 mm Hg (1.3 kPa), and a base deficit that could not be calculated. Full resuscitation was required including chest compressions, epinephrine, umbilical venous catheterization, and normal saline boluses. The infant's Apgar scores were 1, 3, 4, and 4 at 1, 5, 10, and 15 minutes, respectively. Physical examination revealed an appropriately grown (weight 3,915 g) nondysmorphic male infant with severe hypotonia, gray color, and apnea. He developed seizures at 15 minutes, which were treated with phenobarbital. His complete blood cell count was normal. The lactate level at 30 minutes was 21.7 mmol/L. His first arterial blood gas was drawn at 40 minutes and had a pH of 6.68, a  $P_{CO_2}$  of 71 mm Hg (9.4 kPa), a  $P_{O_2}$  of 80 mm Hg (11 kPa), and a base deficit of 23.3. He received therapeutic hypothermia and required assisted ventilation for 48 hours for moderate pulmonary hypertension of the newborn. He developed disseminated intravascular coagulopathy for which a multitude of blood products were provided. Cranial ultrasonography at 48 hours of age showed increased echogenicity suggesting cerebral edema. Magnetic resonance imaging of the brain at 4 days of age showed restricted diffusion in the thalami and putamen bilaterally, suggesting an acute injury.

He was discharged from the hospital at 3 weeks, taking all of his feedings orally. *The plaintiff neonatologist stated that during periods of excessive uterine activity, the fetal reserves were depleted. At the time of the uterine rupture, injury to the brain developed.*

On a 9-year follow-up examination, the child had cerebral palsy, impaired speech, profound developmental delays, and dextroscoliosis.

The obstetrician was sued for not following standard of care, which included:

1. Not noticing tachysystole
2. Not reducing or discontinuing oxytocin when tachysystole developed
3. Not moving faster for a cesarean section at the inception of the second stage of labor.

The hospital was sued because the nurses:

1. Did not reduce or discontinue the oxytocin when tachysystole developed
2. Failed to notify the obstetrician in a timely fashion, when the fetus developed severe variables, which transitioned to bradycardia.

Both the obstetrician and the hospital settled before the case went to trial.

## DISCUSSION

For the fetus to achieve sufficient uptake of oxygen and elimination of carbon dioxide during labor, it is necessary for the contractions to be adequately spaced. Uterine activity causes intermittent interruption of blood flow to the intervillous space, resulting in periodic cessation of blood gas transfer. For adequate exchange of blood gases between the fetus and the placenta, it is necessary for the 1) peak of successive contractions to be spaced further apart than 2 minutes, and 2) baseline of one contraction to the next to be greater than 1 minute.

If the contractions are too frequent, the time during the relaxation phase is insufficient for adequate blood gas exchange. Excessive uterine activity for a prolonged time may result in fetal acidemia. Depending on the reserve of the fetus and the duration of this challenge, this situation can produce varying degrees of compromise and organ injury.

Oxytocin use for induction or augmentation of labor is a common occurrence in labor and delivery. The use of oxytocin is associated with an increased risk of excessive uterine activity. An excessive amount of uterine contractions may result in a significant decrease or interruption of blood flow between the pregnant woman and fetus, directly affecting gas exchange. Oxytocin exposure increases

the risk of tachysystole and the number of events correlates with the oxytocin dose. Fetal heart rate changes occur in a quarter of tachysystole events. The presence of tachysystole increases the chance of neonatal morbidity. In addition, excessive uterine activity has the potential to directly affect the uterus, especially if a prior cesarean section was performed, because the weakened tissue from the uterine scar is vulnerable.

Oxytocin is a high-alert medication, making its administration a significant risk if not properly managed. The Food and Drug Administration issued a black box warning for oxytocin. In 2007, the Institute for Safe Medication Practices, which is an independent, nonprofit organization, placed oxytocin on the list for high-alert medications, a distinction reserved for fewer than a dozen drugs. In 2009 clinical opinion, the American College of Obstetricians and Gynecologists recognized the dangerous propensities of oxytocin and established new guidelines promoting patient safety. Recognizing that if oxytocin is used improperly, it may cause asphyxia and trauma to the fetus, many hospital guidelines include a standardized approach for the administration of oxytocin, including evidence of fetal intolerance to labor augmented by oxytocin hours before the uterine rupture, as seen in the case described herein.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor including reassuring and nonreassuring and indeterminate patterns.

## Suggested Readings

- American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *Obstet Gynecol.* 2009;114(1):192–202
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### ANSWER KEY FOR FEBRUARY 2019 NEOREVIEWS

**Primary Immunodeficiency in the NICU:** 1. B; 2. D; 3. A; 4. B; 5. B.

**Perinatal HIV Transmission: Missed Opportunities and Proposed Solutions:** 1. A; 2. E; 3. C; 4. D; 5. A.

## Legal Briefs: Tachysystole, Uterine Rupture, and a Bad Outcome

Maureen E. Sims

*NeoReviews* 2019;20:e110

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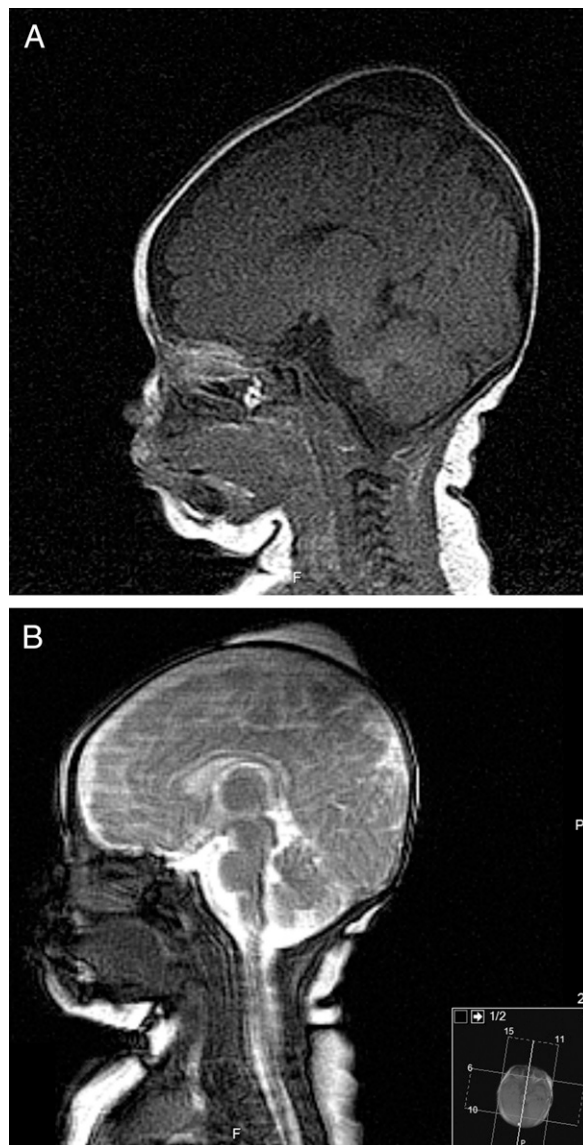
## An Unusual Late Presentation of Swelling over the Head

Fredy David Valero, MD,\* Carlos Castillo, MD,\* Sergey Prokhorov, MD,\* Catalina Marino, MD\*

*\*Lincoln Hospital, affiliated with Weill Cornell Medical College, Bronx, NY*

### THE CASE

A 44-day-old full-term female infant presents to the emergency department (ED) with head swelling (Fig 1).



**AUTHOR DISCLOSURE** Drs Valero, Castillo, Prokhorov, and Marino have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Figure 1.** Magnetic resonance imaging of the head shows a right parietal subgaleal collection crossing the midline and measuring approximately 4.7×3.7×0.8 cm and appears hypointense on the T1-weighted sequence (A) and hyperintense on the T2-weighted sequence (B).

### Prenatal and Birth Histories

- Born via cesarean to a 27-year-old gravida 1, para 0 woman after an uncomplicated pregnancy.
- Estimated gestational age at birth: 41 weeks.
- Intrapartum course significant for arrest of labor with frequent decelerations and subsequent fetal scalp monitor placement; vacuum and forceps were not used during delivery. Prenatal maternal laboratory findings: group B *Streptococcus* positive; otherwise unremarkable.
- Apgar scores: 9 and 9 at 1 and 5 minutes, respectively.
- Birthweight 3,000 g (21st percentile), length 50.5 cm (54th percentile), head circumference 34 cm (21st percentile).
- Discharged from nursery at 74 hours of age with normal physical examination findings.

### Presentation

The infant was asymptomatic until 41 days of age when the parents noted swelling over the head while changing her diaper. Parents denied head trauma, change in her activity level, fussiness, vomiting, diarrhea, or other symptoms. Because the patient had no other symptoms, the parents did not seek medical attention until 3 days later when they noticed that the swelling did not resolve.

The infant was then evaluated in the ED and admitted at 44 days of age.

Cranial ultrasonography was performed (Fig 2).

### PROGRESSION

#### Vital Signs

- Heart rate: 154 beats/min
- Respiratory rate: 38 breaths/min
- Blood pressure: 89/49 (mean 62) mm Hg
- Oxygen saturation: 98% (in room air)
- Temperature: 99.4°F (37.4°C)

#### Physical Examination

- Current weight 4,660 g (57th percentile), length 53 cm (17th percentile), head circumference 37.5 cm (38th percentile).
- General: Well-appearing infant in no acute distress.
- Head: Open and flat fontanelles. A 7×6 cm, nontender, fluctuant, and soft swelling was present in the right parietal area that extended beyond the midline without tenderness or changes of the overlying skin; no fluid wave was present.
- Oral cavity: Pink mucosa, intact palate, normal sucking
- Lungs: Symmetric, clear to auscultation, without distress
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallops

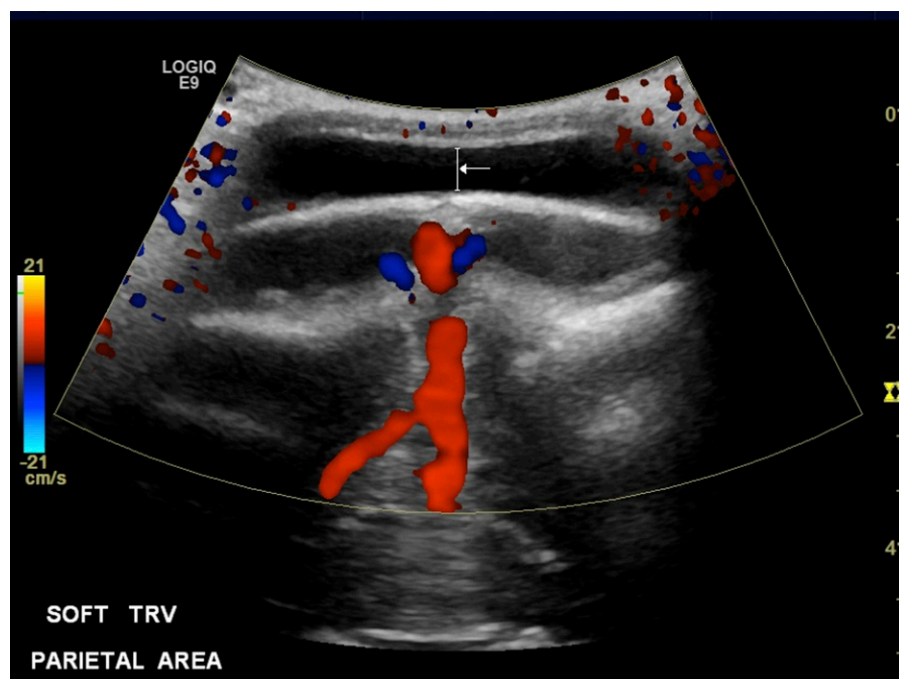


Figure 2. Head ultrasound scan, with the arrow demonstrating a 4.3×2.2×0.5 cm anechoic fluid collection within the scalp in the right parietal region.



Figure 3. Skull radiograph showing scalp swelling and no skull fracture.

- Abdomen: Soft, without tenderness or organomegaly.
- Genitourinary: Normal female genitalia
- Skin: No bruises, rashes, or skin discoloration.
- Extremities: No deformities, capillary refill less than 2 seconds.
- Neurologic: Active and interactive; adequate tone; symmetric Moro reflex and movements.

#### Laboratory Studies

- White blood cell count  $9.9 \times 10^3/\mu\text{L}$  ( $9.9 \times 10^9/\text{L}$ ), with 13.3% neutrophils, 73.2% lymphocytes, and 1.7% eosinophils.
- Hemoglobin: 10 g/dL (100 g/L).
- Hematocrit: 30.2%.
- Platelets:  $445 \times 10^3/\mu\text{L}$  ( $445 \times 10^9/\text{L}$ ).
- Prothrombin time: 10.3 seconds.
- Partial thromboplastin time: 35.7 seconds.
- Basic metabolic panel: Normal.

#### Radiographic Studies

- Magnetic resonance imaging (Fig 1) showed a right parietal subgaleal collection crossing the midline, measuring approximately  $4.7 \times 3.7 \times 0.8$  cm, which was

hypointense on the T1-weighted sequence (Fig 1A) and hyperintense on the T2-weighted sequence (Fig 1B). There was no evidence of intracranial injury.

- Head ultrasonography (Fig 2) showed a  $4.3 \times 2.2 \times 0.5$  cm anechoic fluid collection within the scalp in the right parietal region, which may be related to a sequela of a scalp hematoma but other causes could not be excluded.
- Skull radiography did not show any fractures (Fig 3).

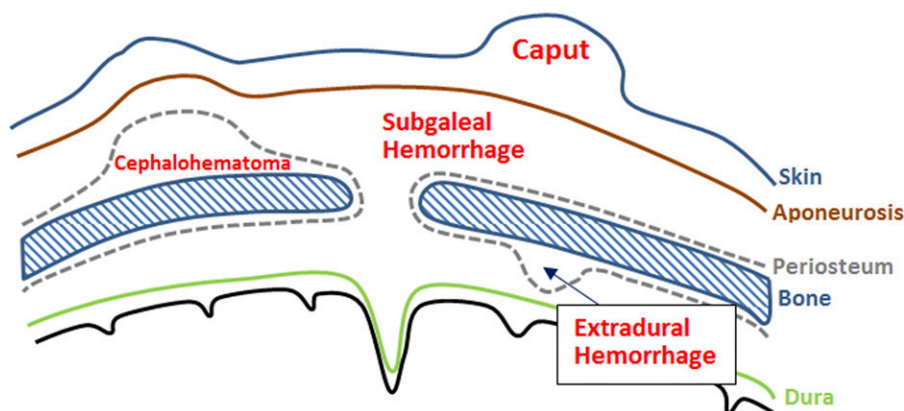
#### Progression

The infant was admitted for clinical observation for concerns of nonaccidental trauma and active bleeding. An extensive evaluation, including prothrombin time, partial thromboplastin time, international normalized ratio, von Willebrand factor, ristocetin cofactor, factor VIII, factor IX, and factor XIII, was within normal limits. A thorough social assessment by a team consisting of a social worker, child protective services, and a child abuse specialist did not identify any potential risk factors for child abuse. Over the 7 days of admission, the infant's scalp swelling decreased in size from  $7 \times 6$  cm to  $5 \times 4$  cm, and remained without tenderness or changes in color or consistency.

TABLE. **Characteristics of Different Types of Swelling over the Head in the Newborn**

	CAPUT SUCCEDANEUM	CEPHALOHEMATOMA	SUBAPONEUROTIC FLUID COLLECTION	
			BLOOD	CSF
Location	Soft tissue	Cranium: periosteum	Epicranial aponeurosis:	periosteum
Incidence (per 10,000 newborns)	520 (6)	100 (1)	1.5 (2)	N/A
Age at onset	0 hours (2)	Several hours (1)	1 day (7)	3.5 (5) to 18 weeks (3)
Regression	2-3 days (2)	3-4 weeks (1)	2-3 weeks (2)	2-24 weeks (3)

CSF=cerebrospinal fluid; N/A=not available.



**Figure 4.** Major cranial layers and extracranial collections. Reprinted with permission from Whitesel E, Brodsky D. Fluctuant mass on an infant's scalp. *NeoReviews*. 2018;19(8):e490–e492.

## DIFFERENTIAL DIAGNOSIS

- Bleeding disorder
- Caput succedaneum
- Cephalohematoma
- Head molding
- Nonaccidental head trauma
- Subaponeurotic cerebrospinal fluid (CSF) collection
- Subgaleal hemorrhage

## ACTUAL DIAGNOSIS

Subaponeurotic fluid collection (SFC) secondary to CSF fistula.

The infant's hemoglobin, hematocrit, and platelet count remained stable. The patient was discharged to the parents once the diagnosis was made and serious intracranial pathologies were ruled out. Two weeks after discharge, the swelling was completely resolved.

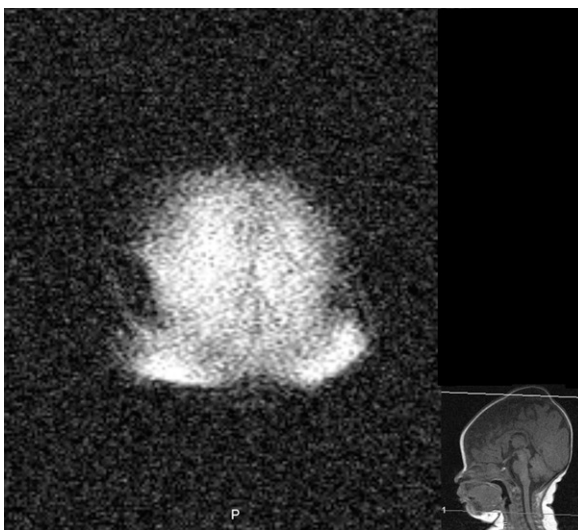
## WHAT THE EXPERTS SAY

Swelling over the head is a common finding in the newborn period. The most common causes include caput succedaneum and cephalohematoma (Table) (Fig. 4). (1)

Infants can also have an SFC, which is defined as an accumulation of fluid between the epicranial aponeurosis and the external layer of the periosteum. Because the fluid is not contained by the periosteum, it crosses sutures and therefore the midline. Collections in the subaponeurotic space can contain CSF or blood. Because the subaponeurotic connective tissue is highly vascularized by the emissary veins, SFC containing blood (also known as a *subgaleal hemorrhage*) is more common than CSF

collections. It has been reported in the literature that the subaponeurotic space can accumulate up to 260 mL of blood, (2) which is enough volume to cause hypovolemic shock and death in a patient of this age. On the other hand, SFC caused by accumulation of CSF is a benign process that resolves spontaneously 2 to 24 weeks after diagnosis. (3) Gradient echo MRI sequence is used to identify blood products in the MRI that appear as hypointense lesions in this sequence. (4) In the current patient, this sequence showed a hyperintense collection in the subaponeurotic region, pointing to a CSF collection as the most likely cause (Fig 5).

Invasive interventions are widely known to cause head injuries in the newborn. Placement of a scalp fetal electrode is a risk factor for developing a CSF SFC. (5) Petraglia et al recently described 4 cases with delayed



**Figure 5.** Brain magnetic resonance imaging gradient echo sequence demonstrating a hyperintense collection in the subaponeurotic space.

presentation of subgaleal CSF collection, all of which had in common the use of scalp fetal monitor during delivery. (5) Schoberer et al (6) demonstrated the presence of  $\beta$ 2-transferrin in fluid aspirates of 3 patients with SFCs.  $\beta$ 2-transferrin is present only in CSF, aqueous humor, and perilymphatic fluid. (6) Although the exact mechanism of appearance is not fully understood, a CSF fistula has been postulated as a possible cause of SFC containing CSF.

In the current case, there was no clinical or laboratory evidence of hemodynamic instability to consider hemorrhage. In addition, the time of appearance and spontaneous regression suggest CSF SFC as the most likely cause of head swelling in this patient. Other differential diagnostic considerations in SFC include molding, caput succedaneum, and cephalohematoma (Table).

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the diagnostic, clinical, and imaging features of extracranial hemorrhage, including cephalohematoma and subgaleal hemorrhage.

- Know the management, complications, and outcomes of extracranial hemorrhage, including cephalohematoma and subgaleal hemorrhage.

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## Telemedicine in Neonatology

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### Education Gap

The use of telemedicine in neonatology is relatively new and is rapidly evolving. It has great potential to increase access to expert care while decreasing costs in areas where access to care is limited. Successful implementation of a telemedicine program requires an understanding of how it has successfully been used, and how it might be used in the future, to increase access to care for neonates across the country. As telemedicine is increasingly used in diverse aspects in neonatology, additional research and evaluation of the effectiveness of telemedicine for neonatal care are required.

### Abstract

Telemedicine is fast becoming integrated into health care as a way to increase access for patients, particularly across the urban/rural divide. Use of telemedicine in neonatology is a newer, yet rapidly expanding modality. This review outlines the history of telemedicine, the evolution of its current uses in neonatology, requirements for starting a telemedicine program, and potential future uses.

**AUTHOR DISCLOSURE** Ms Hoffman and Drs Lapcharoensap, Huynh, and Lund have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

#### ABBREVIATIONS

BIO	binocular indirect ophthalmoscopy
CHD	congenital heart disease
CMS	Centers for Medicare and Medicaid Services
DNV	Det Norske Veritas
eICU	electronic intensive care unit
NRP	Neonatal Resuscitation Program
ROP	retinopathy of prematurity
SPROUT	Supporting Pediatric Research on Outcomes and Utilization of Telehealth
SUNDROP	Stanford University Network for Diagnosis of ROP
VAR	video-assisted resuscitation
VLBW	very-low-birthweight

### Objectives After completing this article, readers should be able to:

1. Describe the historical and current applications of telemedicine in neonatology.
2. Identify challenges to implementing and sustaining a telemedicine program in the NICU.
3. Identify potential future applications of telemedicine in neonatology.

## DEFINITION OF TELEMEDICINE

The American Telemedicine Association defines telemedicine as “the remote delivery of healthcare services and clinical information using telecommunications technology.” (1) The typical setup for an acute care telemedicine program is a “hub-and-spoke” model (Fig 1). The hub is generally an academic medical or tertiary care center, but it can be a smaller hospital. The spoke is the site where the patient is located. This may be a smaller community hospital, a physician’s clinic, or even a patient’s home. (2)

There are 2 main branches of telemedicine: asynchronous and synchronous. Asynchronous telemedicine includes non-real-time (“store-and-forward”) data transfer such as image transfer from one facility to another to be interpreted, electronic mail via secure patient platforms, and remote patient monitoring programs that send patient information to providers on a daily basis for follow-up. Synchronous telemedicine refers to any live (“real-time”), 2-way audio-video connections between providers and patients, or among health care teams caring for patients. (3)

## DRIVERS OF TELEMEDICINE

The goal of telemedicine across all disciplines is to increase access to expert care for patients at some distance from larger tertiary care centers. Telemedicine is also aimed at

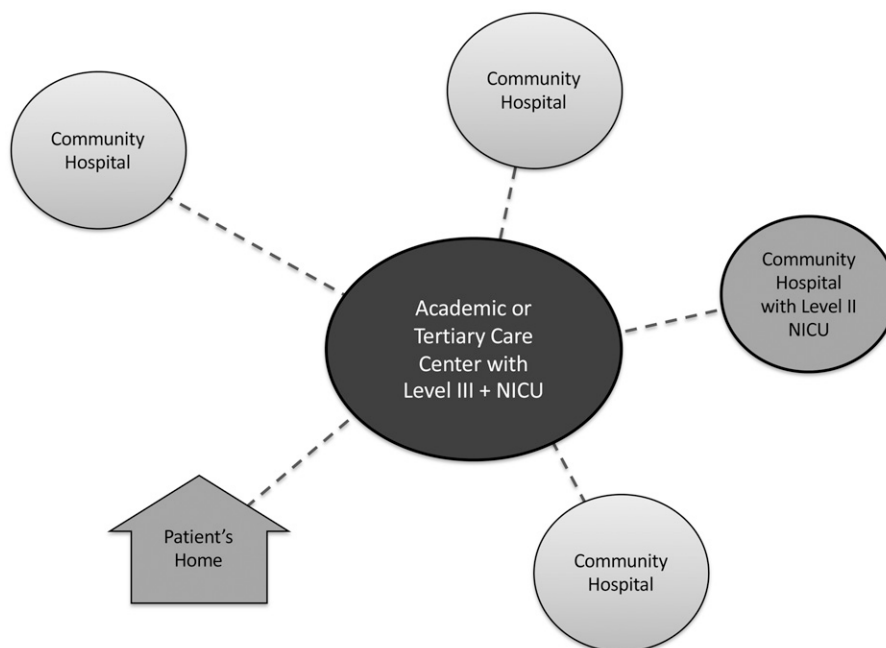
decreasing the costs and risks associated with unnecessary patient transfers to larger tertiary centers, and increasing bed availability at those centers for patients in need of a higher level of care. (4)(5)(6)

Access to expert maternal and neonatal care is pocketed across the United States with the greatest coverage by academic medical centers in urban areas. A recent geospatial study of perinatal services in the United States found that 10% of women of childbearing age must travel to another state to access their closest neonatal or maternal-fetal critical care unit. (7) As with perinatal care, there is incentive for continued regionalization of neonatal care across the country because it is associated with better neonatal outcomes. (8) Especially among infants of lower gestational age (<32 weeks) and very-low-birthweight (VLBW) infants (defined as having birthweights <1,500 g), mortality is lower for infants delivered in hospitals with higher-level NICUs and higher volumes of patients. In this setting of regionalized care, telemedicine is being used to bridge the distance and access gap among urban tertiary centers and community and critical access hospitals. (9)(10)

## HISTORY

### Adult Medicine

Telemedicine began as a program of remote monitoring and care for astronauts in the 1960s. (11) Early technology



**Figure 1.** The hub-and-spoke model of a neonatal telemedicine program. Spoke sites may be community hospitals with basic level I neonatal care, level II NICUs with limited or no subspecialty care, or a patient’s home for follow-up after discharge. Hub sites are typically larger regional care centers with level III or higher NICUs and a wide range of subspecialty and surgical services.

allowed for continuous monitoring of the astronauts' cardiopulmonary health. In addition, the cabin environment, including cabin pressure and levels of carbon dioxide and oxygen, was monitored. The functions that could be monitored increased in complexity over time and with longer space missions. (11)

First piloted in the mid-1990s, store-and-forward technology is now well-established and ranges across all imaging modalities, including radiography, magnetic resonance imaging, and electrocardiography. (12) Currently, the most widespread use for real-time telemedicine is for the evaluation and treatment of adult stroke. In this model, patients at referring (spoke) hospitals are evaluated by a stroke neurologist at a hub site who determines if patient transfer for advanced therapy is appropriate. This technology has decreased both the time to treatment and the number of unnecessary patient transfers to higher levels of care. (13)

### Pediatrics and Neonatology

The top 5 reported uses of telemedicine in pediatrics are in critical care, neonatology, psychiatry, cardiology, and neurology. (14) Initial advances in acute care use have been made in PICUs and emergency medicine, including consultation for trauma, patient transfer decisions, and pediatric resuscitation. (15)(16) In the early 2000s, Kon and Marcin performed a feasibility study of real-time telemedicine allowing pediatric intensivists to consult on live pediatric resuscitations in rural emergency departments. (15) Importantly, they found that the visual assessment of the patient via 2-way video allowed pediatric intensivists to provide more focused care than they could provide over the phone.

In neonatology, the use of real-time telemedicine is varied. As far back as 1998, telemedicine technology was used to introduce neonates to families while they were in the NICU. (17) The feasibility of using the same equipment for real-time medical assessment was examined, but a clear video feed was not technologically available at that time. Feasibility studies since then have mainly focused on the ability of the neonatologist to perform an adequate assessment of the patient over telemedicine, (18)(19) and on the impact of tele-consultation on clinical decision-making. (20)(21)(22)(23) The largest body of research on the use of telemedicine in neonatology is for the diagnosis of retinopathy of prematurity (ROP). (24)(25)(26)(27)(28)(29)(30)(31)(32) Newer uses of telemedicine include real-time and simulated neonatal resuscitations led by a clinician at a remote institution, (22)(23) long-distance education, and remote rounds. (9)(10)(21)(33)

As pediatric telemedicine moves into the mainstream, clinicians are working together to create guidelines and research standards through a group called Supporting Pediatric Research on Outcomes and Utilization of Telehealth (SPROUT). (14) SPROUT recently conducted a survey of health care organizations from 30 states regarding their use of telemedicine in pediatrics. Fifty-six organizations responded to the survey. Twenty respondents had established programs in neonatology and over 10 of the respondents had neonatal pilot projects under way. In this survey, neonatology programs outnumbered pediatric critical care programs. (14) While this is a subset of health care organizations and the results cannot be generalized, it appears that telemedicine for neonatology is rapidly increasing across multiple health care institutions in the United States.

### CURRENT USES

#### Retinopathy of Prematurity

The most studied use of telemedicine in neonatology is for ROP screening (Table 1). ROP is a leading cause of preventable blindness in children in the United States. The high incidence of ROP is thought to be in part due to the improvement in survival of at-risk populations. (24)

Traditionally ROP is diagnosed at the bedside using binocular indirect ophthalmoscopy (BIO), performed by an ophthalmologist. Both a shortage of qualified ophthalmologists who screen for ROP, and the more recent decentralization of medical care for neonates to community and rural hospitals that offer higher-level intensive care for preterm infants, has resulted in a large at-risk population without direct access to ROP screening. Coordination and tracking of care for these infants is complex, and ROP specialists spend great amounts of time and resources to travel to distant sites to provide screening and follow-up using BIO. Therefore, a store-and-forward modality of telemedicine, in which digital fundus images are obtained on site by a trained imager and sent to an off-site ophthalmologist for interpretation, has been used to increase access to ROP screening. (25)

Several small but high-quality studies have examined the feasibility of telemedicine for ROP screening. The bulk of the studies assess the accuracy of digital image interpretation compared with bedside BIO. Reported sensitivities range from 77% to 100% and specificities 90% to 100%, depending on the severity or grade of ROP and postmenstrual age group examined. (26)(27)(28) However, there is wide variability in methodology in these studies.

The largest observational study, by Quinn et al, included more than 1,200 infants (birthweight <1,250 g) from 13



TABLE 1. Current Uses of Telemedicine in Neonatology

USE	DESCRIPTION	REFERENCES
<i>Subspecialty consultation and screening</i>		
Ophthalmology	Retinopathy of prematurity screening via remote digital retinal imaging	24–32
Cardiology	Remote review of echocardiograms by a pediatric cardiologist with store-and-forward technology, or via real-time guided echocardiography	5,6,34
Neurology	Neurologist-led examination of infants with neurologic concerns, via real-time telemedicine	19
Genetics	Geneticist-led real-time examination of infants with dysmorphisms for genetics consultation and evaluation	19
Surgery	Surgical consultation via either real-time or store-and-forward telemedicine for development of plan and follow-up	12
<i>In the NICU and beyond</i>		
Remote rounds	Bedside rounds facilitated by on-site care team with remote real-time telemedicine led by a neonatologist	33, 36
Family involvement	Family access to an informational website, videoconferencing presence at daily rounds, and discharge preparation	17, 37
NICU follow-up	Real-time telemedicine visits with a midlevel clinician after NICU discharge	37, 38
<i>Neonatal resuscitation</i>		
Video-assisted resuscitation	Neonatologist-led video-assisted resuscitation for higher-risk deliveries at community hospitals	23, 42, 43
Simulation education	Use of telemedicine for video-assisted resuscitation simulation for community hospital provider training	22

centers in the United States and Canada. (29) The study included examination of each patient using both traditional bedside BIO and digital retinal imaging by a trained non-physician imager, with subsequent interpretation of the images by trained nonphysician readers. Trained non-physician imagers and readers included neonatal nurse practitioners, NICU nurses, various ophthalmologic technicians, and even some “individuals with nonclinical backgrounds.” (29) In this study, bedside BIO was performed by an ophthalmologist. Referral-warranted ROP (defined as zone I ROP, stage 3 or worse ROP, or plus disease) was diagnosed with 90% sensitivity and 87% specificity using the telemedicine-based imaging compared with bedside ophthalmoscopy. Importantly, the group demonstrated that high sensitivity can be achieved with telemedicine-based screening even when images are obtained and interpreted by trained nonphysicians. (29)

One of the most extensive telemedicine-based ROP screening programs is the Stanford University Network for Diagnosis of ROP (SUNDROP). A recently published retrospective analysis of a 6-year experience with the

program evaluated more than 600 infants who had more than 2,100 separate examinations. (30) They reported a treatment-warranted ROP incidence of 3.6%, with 100% sensitivity and 99.8% specificity, using telemedicine-based retinal imaging compared with bedside BIO.

Two separate cost decision analyses, one in the United States and one in the United Kingdom, found that telemedicine is more cost-effective than bedside ophthalmoscopy. (31)(32) These 2 studies demonstrate that telemedicine-based ROP screening, when used in different health care systems with different delivery and payment structures, can similarly reduce costs associated with ROP diagnosis and treatment.

Based on the evidence in 2014, the American Academy of Pediatrics Joint Technical Report on Telemedicine for Evaluation of Retinopathy of Prematurity concluded that “telemedicine serves as a useful adjunct to but not a replacement of BIO.” (25) It is likely that the vast and urgent need for ROP screening prompted quick initiation and expansion of telemedicine ROP screening programs, without true standardization or a clear plan for the study of their impact. More

research is needed on all facets of telemedicine-based ROP screening programs, including clinical outcomes, access to care, standardization of protocols and performance, and cost-effectiveness. (24)

### Echocardiography to Diagnose Congenital Heart Disease

Telemedicine has been used to facilitate consultation with trained pediatric cardiologists for neonates and infants with suspected congenital heart disease (CHD) at hospitals without pediatric cardiology services. In the case of infants with respiratory distress or hypoxemia, distinguishing between primary lung disease and primary cardiac disease can be clinically challenging. Many infants who have a cardiac murmur or significant respiratory distress have mild or no congenital cardiac disease. These infants are often transported to a higher level of care for evaluation when they could remain at the referring hospital for respiratory care, and followed up after NICU discharge. (6) To improve access to pediatric cardiology consultation, groups have used both store-and-forward and real-time telemedicine to allow expert interpretation of echocardiography performed by remote sonographers. (6)(34)

The largest study of store-and-forward technology for echocardiogram interpretation is a multicenter trial of infants younger than 6 weeks who were referred to a tertiary care center with cardiology services for a “heart murmur” or to “rule out congenital heart disease.” (6) The study compared 337 matched pairs of infants at referring hospitals with and without telemedicine services, who were ultimately diagnosed with mild heart disease or no CHD. Infants at hospitals with telemedicine services had significantly shorter times to diagnosis, lower rates of transport to a tertiary care center, decreased hospital and intensive care lengths of stay, and decreased exposure to unnecessary treatments, such as inotropic support. This study demonstrated that telemedicine cardiology and echocardiogram review services have the potential to significantly reduce unnecessary transport of infants with mild or no CHD.

Grant et al conducted a prospective study of “the accuracy of remote diagnosis of CHD” using real-time guided echocardiography. (34) They demonstrated that live echocardiography with guidance from a pediatric cardiologist via telemedicine resulted in an accurate diagnosis in 96% of cases, when compared to in-person examination and echocardiography by the same cardiologist in the same patient. The telemedicine-guided assessments also prevented unnecessary transfer of patients without significant CHD to a higher level of care. These studies demonstrate that using telemedicine for echocardiogram interpretation or live guidance of echocardiography can increase diagnostic

accuracy, decrease unnecessary care, and reduce the transport of neonates with mild or no heart disease. (6)(34)

### Other Subspecialty Consultation

Few groups have published data on the utilization of telemedicine to complete remote patient evaluations for neonatal subspecialty consultation. Robie et al examined the usefulness of telemedicine-based consultation for surgical problems in infants in the NICU. (12) In that small prospective study, 19 infants were randomized to in-person pediatric surgery consultation or to either real-time or store-and-forward telemedicine modalities. They reported accurate diagnosis via telemedicine of various common neonatal surgical problems, including poor feeding necessitating gastric tube insertion, necrotizing enterocolitis, abdominal wall defects, imperforate anus, and possible intestinal obstruction presenting as bilious emesis. In each case studied, telemedicine consultation was sufficient to establish a care and follow-up plan. In select cases, telemedicine consultation was able to reduce the need for additional diagnostic studies. (12)

A small prospective study of 20 infants in the NICU found that telemedicine could be used by consulting neurologists or geneticists to accurately complete neurologic and dysmorphology examinations. (19) Off-site examiners used the aid of an on-site clinician to perform maneuvers and optimize visualization with the telemedicine system. Telemedicine evaluations of infants resulted in 93% accuracy for dysmorphology examination findings and 92% accuracy for neurologic examination findings with the first attempt, when compared with examination of the same infant by the same evaluator at the bedside after telemedicine examination. The authors report in detail their discovered methods for optimizing visualization of infants, to increase accuracy of telemedicine-based examination.

Taken together, these studies suggest the ability of telemedicine to deliver subspecialty care for neonates in centers without subspecialty services and to facilitate timely diagnosis and care plan formulation. (12)(19) Telemedicine consultation may also reduce the need to transport infants for specialty diagnostic imaging, though further research is needed to confirm this benefit.

### Remote Rounds

Research in adult medicine has demonstrated that daily critical care services can be delivered using telemedicine, but telemedicine for real-time delivery of care is understudied in neonatology. (35) Two groups have reported on their use of real-time telemedicine to facilitate care for premature infants at lower-level neonatal care centers. (33)(36)

Makkar et al describe their use of a “hybrid” telemedicine system, in which care was provided at a level II NICU in a medically underserved area by 24-hour neonatal nurse practitioner coverage, with an on-site neonatologist 3 days per week and a telemedicine-based neonatologist making rounds from a level IV NICU the remaining days. (33) The retrospective study compared outcomes for infants born at 32 to 35 weeks’ gestation at the level II NICU with comparable infants transported to the level IV NICU. They demonstrated noninferiority of the hybrid design of making telemedicine rounds at the level II NICU for outcomes including type and duration of ventilation and duration of noninvasive ventilation. Surprisingly, some outcome measures (length of stay, time to full enteral feedings, total days of supplemental oxygen) were better for infants treated via telemedicine. The authors speculated that the stress of transport might result in worse outcomes; however, it is not clear if there was a significant difference between the groups in terms of severity of illness.

In a prospective feasibility study, Garingo et al compared the outcomes for infants born at 32 to 35 weeks’ gestation at the same academic-affiliated level IIIA NICU managed by either the on-site neonatologist or an off-site neonatologist using a telemedicine robot to conduct daily bedside rounds. (36) There were no observed differences in postmenstrual age at discharge, length of stay, respiratory support, or number of days on antibiotics, between the 2 study groups. Time spent on patient encounters for the group making telemedicine-based rounds was significantly longer than the group making standard rounds, and technical difficulties were reported in 10% of the telemedicine encounters, mostly because of poor audio/visual quality with the telemedicine robot. (36)

### Neonatal Follow-up Care and Family Involvement

A few groups have described the use of telemedicine and internet-based tools to enhance family education and involvement for NICU patients. (37)(38) In 2000, Gray et al described the earliest example of a combined “videoconferencing” and web-based program that delivered virtual visits and education for parents during their infant’s hospitalization. (37) Named “Baby CareLink,” the program consisted of web-based software offering daily clinical updates, photos of the infant obtained by clinical staff, a message center for parents to communicate with care providers, and focused preparation for discharge from the hospital. It also included teleconferencing to facilitate family participation in bedside rounds from a distance.

A prospective randomized trial comparing VLBW infants receiving standard care with infants and families receiving

enhanced care via the Baby CareLink system demonstrated that families using Baby CareLink reported receiving better care (with fewer reported problems) and were more satisfied with the care their infants received. (37) There was no difference in hospital length of stay overall, but there was a trend toward shorter length of stay for infants with birthweights less than 1,000 g in the Baby CareLink group. Among the control group, 20% of infants were transferred to community hospitals for continuation of care before discharge from the hospital, whereas 100% of the Baby CareLink infants were directly discharged from the hospital.

Though the Baby CareLink study identified home NICU follow-up via telemedicine as a capability of the service, no data were reported in that published study. (37) A more recent study in Sweden compared outcomes of infants discharged with standard home health visits with outcomes of infants discharged with telemedicine follow-up (video conference visits and an informational website) in addition to the standard home health visits. (38) Parents reported high satisfaction with the telemedicine follow-up service. Infants with telemedicine follow-up needed fewer scheduled home health visits and had fewer emergency visits than the control group, though the numbers were small. More research is needed on both telemedicine-based rounds and neonatal follow-up after discharge to determine efficacy, safety, and cost-effectiveness, as well as to establish best practice guidelines.

### Neonatal Resuscitation and Simulation Training

A newer use of telemedicine in neonatology is video-assisted resuscitation (VAR). In VAR, a neonatologist leads the delivery room team through a resuscitation using a real-time connection. In hospitals with low-risk deliveries, clinicians encounter fewer neonates requiring intervention at delivery compared with larger hospitals with high-risk delivery services. In such locations with low-frequency high-risk events, the scarcity of neonatal resuscitations may result in minimal use of Neonatal Resuscitation Program (NRP) skills by team members. It is well-established that NRP skills deteriorate rapidly after certification in the absence of subsequent skills refreshers or skills utilization. (39) When used infrequently, commonly missed neonatal resuscitation skills are the predelivery equipment check, the initial steps of NRP, and troubleshooting positive pressure ventilation.

Airway management has been identified as a critical, yet complex component for the success of neonatal resuscitation. (40)(41) Fang et al demonstrated similar findings during a simulated VAR study at the Mayo Clinic. (22) Study participants were presented with an identical resuscitation simulation scenario and were randomized to

participate with or without VAR. Providers receiving real-time video assistance from a neonatologist were able to manage the airway more effectively and more quickly than providers in the control group. VAR also eliminated unnecessary intubation, because all providers receiving assistance were able to establish effective ventilation with a bag and mask. The evidence of change in airway management during a simulated VAR demonstrates potential benefits of real-time VAR in neonatology. An example of a telemedicine setup for VAR simulation for training purposes is depicted in Fig 2.

In 2016, Fang et al published a feasibility study of a neonatal VAR program using a hub-and-spoke model. (23) Nearly one-third of neonates stayed in their local hospital, which decreased medical costs, prevented unnecessary transfers, and prevented separation of the mother and infant. Teamwork between the hub and spoke sites was rated as “high,” however, video quality was found to be faulty in nearly one-third of cases. In a follow-up study, comparison of technology solutions found that for VAR, a telemedicine cart with stable internet connection was superior to consumer-grade technologies using Wi-Fi. (42) The acute nature of VAR requires equipment that is unlikely to falter when used. Increasing reliability of audio-video technology improves the viability of a neonatal VAR program.

Currently there are few studies looking at outcomes of VAR for neonates. A retrospective cohort study found that VAR significantly increased the quality of resuscitation, as determined using a point scale measuring the number of clinically indicated processes completed by the team during resuscitation. (43) The greatest differences in VAR quality compared with the quality of non-VAR was found in neonates of less than 37 weeks’ gestation.

As described by Lapcharoensap and Lee, resuscitation of neonates in the delivery room creates a complex

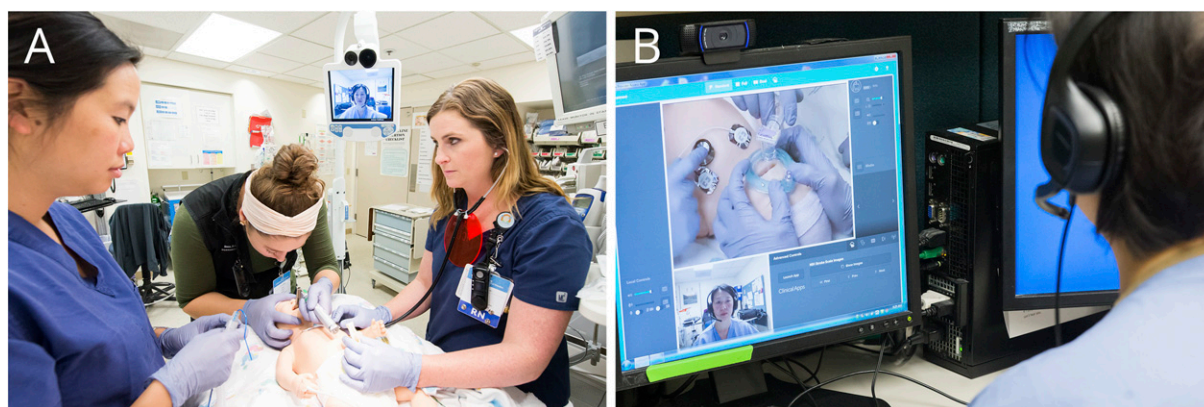
environment with multiple teams and disciplines present. (40) The addition of telemedicine increases the complexity because the clinician leading the resuscitation is not physically in the room. In addition, the resuscitating team may not frequently perform neonatal resuscitation, increasing the potential for skill deterioration and miscommunication. (39) Recommendations for quality improvement in the delivery room, such as code cart standardization, supply checklists, and briefings before birth, can be applied to telemedicine as well. (40) Quality improvement efforts should include both spoke and hub clinicians to ensure good communication and teamwork. (44) At the Oregon Health and Science University, real-time telemedicine briefing before higher-risk deliveries at spoke sites is becoming standardized within a quality improvement framework. An example of a telemedicine-based briefing using a checklist before birth is shown in Fig 3.

## INITIATING A TELEMEDICINE PROGRAM

Considerations for initiating a telemedicine program include identification of use case, understanding of state and federal regulations and requirements, the cost and revenue realities of the program, and program evaluation (Table 2). Regulations and laws are rapidly changing and many policies are state-specific. It is important for clinicians and organizations to understand the state licensing and reimbursement laws applicable to the state in which they are practicing telemedicine. (45)

### Use Case

The critical first step in initiating any telemedicine program is determining the use case, because that will define the area of telemedicine under which the program falls. The use case describes the end goal of the telemedicine program,



**Figure 2.** A neonatologist-led video-assisted resuscitation simulation exercise from the viewpoint of A) the spoke site and B) the hub site. (Photography by Aaron Bieleck, Oregon Health and Science University.)





**Figure 3.** A) The hub site neonatologist, and B) the spoke site clinical team complete a clinical briefing and equipment setup checklist before a higher risk delivery simulation. (Photography by Aaron Bieleck, Oregon Health and Science University.)

workflows, and how any technology will be used. (46) This will then affect reimbursement, licensing, and credentialing requirements, and what technology to purchase. Purchasing telemedicine equipment without a clear understanding of its purpose may result in unused equipment or a need to buy additional equipment to meet future needs. The use case should address a well-defined need with specific goals and be the driving force behind any programmatic decisions. In general, telemedicine use cases are focused on increasing access to and/or decreasing costs of medical care. (16)

### Licensing, Credentialing, and Accreditation

State boards require that the clinician be licensed in the state where the patient is located at the time of the visit. (45) In addition, clinicians will need to be credentialed at each hospital at which they provide telemedicine consultation. (3) There are guidelines for credentialing by proxy put forth by accreditation programs such as the Centers for Medicare and Medicaid Services (CMS), The Joint Commission, and Det Norske Veritas (DNV). (3)(47) Institutions should ensure that their telemedicine credentialing process meets the requirements of their accrediting body and CMS before engaging in telemedicine. Licensing and credentialing barriers affect the scalability of individual telemedicine programs. (3)

Currently, accreditation guidelines of The Joint Commission and DNV focus on credentialing of telemedicine providers, with the understanding that care provided via telemedicine meets the same standards and guidelines

as in-person care. (3)(47) Program evaluation and quality review should include an examination of whether this standard is being met. In the past, The Joint Commission proposed guidelines specific to quality of care in telemedicine. Although those guidelines were not implemented, there is potential for accreditation requirements for telemedicine programs in the future. (48)

### Cost and Revenue

Reimbursement for telemedicine can be complex, and varies by use case, type of connection, patient payer, and state laws. The Federation of State Medical Boards has compiled a list of state licensure and reimbursement requirements. (45) Lower reimbursement rates are a barrier to scalability of programs. The monetary value of telemedicine is instead often calculated by cost savings resulting from fewer patient transfers, (4)(6)(16)(23) emergency department visits, (5) and other health care resource use. (5) (6)(20) When looking at the sustainability of a program, it is important to understand both start-up and maintenance costs. When applying for grant funding for program initiation, there should be a maintenance plan for when the grant funds have been exhausted.

### Program Evaluation

New programs need to be evaluated to ensure that they are effective in meeting the outlined goals. The National Quality Forum has provided guidelines for developing a metrics framework for telehealth programs. (49) Creating and

TABLE 2. **Considerations When Initiating a Telemedicine Program**

PROGRAM COMPONENT	CONSIDERATIONS AND ACTIONS	REFERENCES
Establishing a use case	<ul style="list-style-type: none"> <li>• Determine goals and desired outcomes</li> <li>• Identify program drivers</li> </ul>	16, 46
Licensing, credentialing and accreditation	<ul style="list-style-type: none"> <li>• Ensure all providers are               <ul style="list-style-type: none"> <li>◦ licensed in state patient is located at time of visit</li> <li>◦ credentialed at site of patient service</li> </ul> </li> <li>• Ensure that all care provided by telemedicine meets the same standards as in-person care</li> </ul>	3, 45, 47
Cost and revenue	<ul style="list-style-type: none"> <li>• Determine cost to set up and maintain program</li> <li>• Determine potential revenue from program               <ul style="list-style-type: none"> <li>◦ Reimbursement laws vary by state</li> <li>◦ Medicare reimbursement rules are strict and change yearly</li> <li>◦ Include cost savings and reduction in resource utilization as potential value</li> <li>◦ System revenue may be appreciated downstream due to increased referrals of complex patients and/or better utilization of services/beds</li> </ul> </li> <li>• Consider grants as source of start-up funds</li> <li>• Identify long-term funding mechanism</li> </ul>	4–6, 16, 20, 23
Program evaluation	<ul style="list-style-type: none"> <li>• Evaluate outcomes and goal achievement               <ul style="list-style-type: none"> <li>◦ Track program utilization and patient transfer rates</li> <li>◦ Ensure quality improvement initiatives are cross-institutional</li> </ul> </li> <li>• Review costs and benefits of program</li> </ul>	10, 44, 49

maintaining strong partnerships by including spoke sites in any evaluation is paramount. (10)(44) Program sustainability requires engaged clinician and staff groups at all institutions involved.

## FUTURE OF TELEMEDICINE IN NEONATOLOGY

A recent advancement of telemedicine in the adult and pediatric populations is the development of more proactive models of caring for critically ill patients in the form of an electronic intensive care unit (eICU). (50) In an eICU, a team of ICU nurses and intensivists monitors multiple ICU locations. Using algorithms and video technology, the remote team works with on-site providers to proactively care for patients. This model could be implemented in level II community hospital NICUs. It is feasible that a hybrid eICU program might be considered as part of the bedside rounds model explored by Makkar et al. (33)

Another area of expanding telemedicine use is VAR, as described by Fang et al. (22) Although there are standard guidelines for neonatal resuscitation, there are no guidelines for conducting NRP via telemedicine, or for guiding providers through acute nondelivery resuscitation consultations. Each telemedicine program is variable in design, workflow, and evaluation of outcomes. There is a lack of data on program experiences with telemedicine use to facilitate

resuscitation of the critically ill neonate, and on the outcomes of those infants receiving care assisted by telemedicine. To ensure the highest quality of VAR and neonatology consultation via telemedicine, future research should focus on establishing best-practice guidelines and standardization of programs.

## SUMMARY

Telemedicine has been shown to increase access to expert care for neonates, reduce unnecessary patient transport, and therefore decrease mother-infant separation. With the correct workflows and partnerships in place, telemedicine complements the regionalization of specialty neonatal care by ameliorating access issues. It is important for any institution that implements a telemedicine program to understand the use case, regulatory requirements, and funding, and have a plan for program evaluation and sustainability.

Telemedicine in neonatology is rapidly expanding, and the increase in the number and scope of telemedicine programs is outpacing research and standardization. Through networks such as SPROUT, clinicians using telemedicine are working to understand the outcomes of effective telemedicine to inform the creation of national practice standards.

# American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the issues in the organization of perinatal care (eg, regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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**Historical Perspectives: Telemedicine in Neonatology**  
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# When to Include a Lumbar Puncture in the Evaluation for Neonatal Sepsis

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## Education Gap

Infants younger than 1 month are at risk for meningitis and may not present with classic signs such as seizures or a bulging fontanelle. Thus, a lumbar puncture should be considered during an evaluation for sepsis in newborns in specific scenarios. While the presence of bacteremia increases the likelihood of meningitis in infants, approximately one-third of cases of meningitis occur in the setting of negative blood cultures.

## Abstract

Meningitis is a devastating infection in infants and is linked to adverse long-term outcomes. The prevalence of meningitis is variable and depends on gestational age, postnatal age, and clinical setting. Early diagnosis and treatment with appropriate antibiotics are crucial to decrease the risk of morbidity and mortality. Lumbar punctures are essential for the diagnosis of meningitis, but clinicians may defer lumbar puncture if the risk for meningitis is low or if there are substantial concerns regarding the risk associated with the procedure. Awareness of the epidemiology and microbiology of meningitis in infants, as well as valid contraindications to performing a lumbar puncture, is necessary to avoid missed diagnoses and procedure-related adverse effects.

**AUTHOR DISCLOSURE** Drs Aleem and Greenberg have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## Objectives After completing this article, readers should be able to:

1. Incorporate current evidence to identify infants in the NICU and the outpatient setting who should undergo a lumbar puncture in the evaluation for suspected sepsis.
2. Review the risks and contraindications associated with performing a lumbar puncture in infants.
3. Discuss challenges in the interpretation of cerebrospinal fluid parameters in the setting of absent or uninterpretable cerebrospinal fluid cultures.

### ABBREVIATIONS

CSF	cerebrospinal fluid
ELBW	extremely low birthweight
EOS	early-onset sepsis
GBS	group B <i>Streptococcus</i>
LOS	late-onset sepsis
LP	lumbar puncture
NICE	National Institute for Health and Care Excellence
PCR	polymerase chain reaction
RBC	red blood cell
VLBW	very low birthweight
WBC	white blood cell

## INTRODUCTION

Meningitis is a devastating infection in infants that is associated with substantial mortality and morbidity. In extremely low-birthweight (ELBW) infants, meningitis is associated with long-term morbidities, including cerebral palsy and neurodevelopmental impairment. (1) The incidence of neonatal meningitis in underdeveloped countries ranges from 0.8 per 1,000 live births in the first week after birth to 6.1 per 1,000 live births during the first 3 months of age, with a mortality between 40% and 58%. (2) In developed countries, the incidence is lower, with estimates around 0.3 per 1,000 live births. (3)

Establishing the diagnosis of meningitis in infants can be challenging. The **initial signs** of neonatal meningitis, such as **temperature instability, lethargy, apnea, and bradycardia**, are often subtle and nonspecific and may occur as a result of other noninfectious etiologies. (4) Classic meningitic signs, such as bulging fontanelle and seizures, are usually found later in the course of illness. (5) Adding to the difficulty of diagnosis is the variability in signs of meningitis according to birthweight and degree of prematurity. In a study comparing clinical signs of meningitis in infants with birthweights greater than 2,500 g (n=53) with those less than 2,500 g (n=34), the most commonly occurring signs in infants **greater than 2,500 g** were **fever, irritability, seizures, and bulging fontanelle**, whereas infants **less than 2,500 g** were more likely to present with **apnea, jaundice, and abdominal distention**. (5)

The most reliable way to diagnose meningitis is by obtaining a cerebrospinal fluid (CSF) specimen for analysis via a lumbar puncture (LP). (6) If the CSF specimen is obtained before the initiation of antibiotics, the causative pathogen can be identified and the appropriate antibiotic therapy can be determined. (6) However, an LP is not performed in approximately 30% to 70% of infants being evaluated for early- and late-onset sepsis, respectively, in the NICU. (7)(8) The decision to defer an LP is often based on a lack of clinical signs of meningitis and concerns about the risks associated with the procedure. However, these concerns must be weighed against the consequences of missing the diagnosis of meningitis due to an incomplete evaluation. In this review, we summarize the literature regarding the indications for obtaining an LP specimen in infants and provide recommendations for performing an LP in the evaluation of neonatal sepsis.

## VULNERABILITY OF INFANTS TO MENINGITIS

Newborns have an “antigen-inexperienced” immune system, with **deficiencies in all major arms of immunity**, including **phagocytic function**. Those born prematurely also lack protective maternal antibodies, which do not cross the

placenta before **32** weeks of gestation. (3) Altogether, these deficiencies lead to an increased susceptibility to invasive pathogenic infections. (3)

When bacteria enter the CSF of an infant, a large release of inflammatory mediators and **increased permeability of the blood-brain barrier** results in meningitis. (9) Host defense mechanisms, such as immunoglobulins, complement, and phagocytes, are unable to penetrate the blood-brain barrier, leading to unregulated bacterial replication and brain injury. (9) The presence of invasive foreign devices, such as endotracheal tubes, arterial or venous access catheters, and intracranial ventricular devices, places infants at an increased risk for infections. (10) Intracranial ventricular devices, including ventricular access devices such as ventricular reservoirs and shunts, are particularly high risk because of their presence in the central nervous system. The incidence of meningitis ranges from 7% to 11% in infants with such devices. (11)

In response to infections such as meningitis, infants have the ability to mount an **overwhelming systemic inflammatory response** that can cause further clinical decompensation with resulting brain injury and multiorgan failure. This complex interaction among infection, inflammation, and other comorbidities has a profound impact on future neurodevelopmental outcomes in infants. (1) Given the high likelihood of poor outcomes, early diagnosis and initiation of appropriate therapy for meningitis are critical.

## LP IN THE EVALUATION FOR EARLY-ONSET SEPSIS

Early-onset sepsis (EOS) in infants is defined as an infection in the blood or CSF occurring **within the first 3 to 7 days after birth**. (7)(12) In the United States, the incidence of EOS is low, ranging from approximately 0.77 to 0.98 per 1,000 live births, with the highest incidence seen among the most premature, low-birthweight infants. (7)(13) The incidence of culture-confirmed EOS in developing countries ranges from 2.2 to 9.8 per 1,000 live births. (14) Despite the widely prevalent use of intrapartum chemoprophylaxis to reduce vertical transmission of invasive group B streptococcal (GBS) infection, **GBS** continues to remain **the most common cause of EOS and associated meningitis** in infants and is isolated in ~40% of cases of EOS; **Escherichia coli** is the **second** most common cause of EOS. (7) Among preterm infants, *E coli* has emerged since the 1990s as the most common pathogen responsible for EOS and meningitis. (15)

Although definitive diagnosis of meningitis requires obtaining a CSF specimen, the use of LP remains **controversial** in the evaluation for EOS and there is great variation in practice among centers. (16) Infants often undergo

evaluation for meningitis because of maternal risk factors, such as 1) maternal GBS colonization; 2) rupture of fetal membranes for over 18 hours; 3) maternal fever; 4) foul-smelling amniotic fluid; 5) unexplained persistent fetal tachycardia; and 6) elevated maternal white blood cell (WBC) count. (17)

Overall, the available literature suggests that the risk of early-onset meningitis in asymptomatic infants is low (Table 1).

The 2012 recommendations by the Committee on Fetus and Newborn (17) suggest performing an LP in the evaluation of EOS in 1) any infant with culture-positive bacteremia; 2) infants with a clinical course or laboratory data suggestive of sepsis; and 3) infants who do not show any clinical improvement with initial antimicrobial therapy.

Culture-positive bacteremia is a clear indication for an LP, because up to 25% of infants with bacteremia have concurrent meningitis. (18)

Identifying a “clinical course... suggestive of sepsis” can be more challenging. Signs of sepsis in infants can be subtle and include lethargy, temperature instability, apnea, and

bradycardia. (4) While respiratory symptoms are also considered to be potential signs of sepsis, the yield of LPs in infants who undergo evaluations for respiratory symptoms on admission is low. (19)(20) In a retrospective study of infants between 27 and 36 weeks’ gestational age who were admitted with respiratory symptoms, only 4 cases of culture-confirmed meningitis were found in the 1,495 infants who underwent an LP. (19) Similarly, a study of 238 infants born between 23 and 40 weeks’ gestation who had respiratory distress and were evaluated for sepsis within 24 hours after birth did not find any cases of culture-confirmed meningitis in the 203 infants who underwent an LP. (20)

In summary, it is appropriate to defer an LP in asymptomatic infants who are being evaluated solely because of maternal risk factors (Figure). In infants whose symptoms are thought to be related to a noninfectious cause, a selective approach is prudent and LPs can be reserved for those with culture-positive bacteremia or those showing clinical signs and symptoms of severe sepsis. (21) Adequate treatment for meningitis requires a longer duration of antibiotics with high CSF penetration; therefore, in infants who continue to

**TABLE 1. Role of Lumbar Punctures in the Evaluation for Early-onset Sepsis**

STUDY	POPULATION	RESULTS
Johnson et al, 1997 (54)	5,135 symptomatic and asymptomatic term infants, ≥37 weeks’ gestation, evaluated for maternal risk factors, with positive blood and/or cerebrospinal fluid cultures in the first 7 days of age	11/1,712 (0.6%) symptomatic infants had meningitis 0/3,423 (0%) asymptomatic infants had meningitis
Fielkow et al, 1991 (55)	1,073 symptomatic and asymptomatic infants with an LP in the first 7 days of age	13/789 (1.6%) symptomatic infants had meningitis 0/284 (0%) asymptomatic infants had meningitis
Schwersenski et al, 1991 (32)	712 infants ≤7 days of age who had an LP	1/712 (0.1%) infants had culture-positive sepsis with concomitant meningitis
Visser and Hall, 1980 (21)	323 cultures obtained from 400 infants of 25–42 weeks’ gestation, with birthweights of 634–5,650 g, who were evaluated in the first 72 hours of age	6/19 (32%) cases of early-onset sepsis were associated with meningitis
Weiss et al, 1991 (19)	1,495 preterm infants, from 27–36 weeks’ gestation, with respiratory distress who underwent an LP as part of sepsis screen	4/1,495 (0.3%) infants had true meningitis
Eldadah et al, 1987 (20)	203 infants, 23–40 weeks’ gestation, admitted with respiratory distress with an LP within 24 hours of age	0/203 (0%) infants had meningitis
Ansong et al, 2009 (30)	13,495 infants who underwent at least 1 LP within 7 days of age	22/155 (14%) infants with early-onset GBS sepsis had meningitis
Ajayi and Mokuolu, 1997 (31)	Phase 1: 263 infants with suspected sepsis, and those with risk factors for sepsis who had an LP within 72 hours of age Phase 2: 50 infants with signs of severe sepsis who had an LP within 72 hours of age	0/313 (0%) infants <72 hours of age had meningitis 3 times fewer LPs were performed in phase 2 than in phase 1

GBS=group B Streptococcus; LP=lumbar puncture.

clinically worsen despite standard antimicrobial therapy for sepsis, an LP may be necessary to prevent missed or partially treated cases of meningitis. (17)

## LP IN THE EVALUATION FOR LATE-ONSET SEPSIS IN THE NICU

Late-onset sepsis (LOS) is commonly defined as systemic infection occurring beyond the first 72 hours after birth, with a peak incidence between the 10th and 22nd day of age. (22)(23) Gram-positive organisms are the most commonly isolated pathogens in LOS (63%–70%), with coagulase-negative *Staphylococcus* being predominant (53%–78%), followed by gram-negative organisms (19%–25%), including *E. coli* (6%–8%) and *Klebsiella* (5%–6%). (8)(22)(23)(24) In addition, invasive candidiasis occurs in up to 9% of ELBW infants, with a mortality rate of up to 57% in infants in whom *Candida* is isolated from more than 1 body fluid specimen. (25) The prevalence of LOS in the NICU ranges from 17% to 38% and is higher in more premature infants (24)(26); other risk factors for LOS include long-term mechanical ventilation and central lines, failure of early breast milk feeding, prolonged parenteral nutrition, and length of hospital stay. (22)(24)(27) The presence of intracranial

ventricular devices confers an additional risk of developing meningitis. (10)

LOS is most commonly found in premature infants, and its incidence is inversely related to birthweight and gestational age. (28) Meningitis occurs much more commonly in infants with LOS compared with infants with EOS, and LOS-associated meningitis is more likely to present with symptoms. (29)(30) In a prospective study carried out over 1 year in India, 23% of 102 infants evaluated for LOS were diagnosed with meningitis. (29) In addition, the risk for meningitis increases with increasing postnatal age; the incidence is as high as 10% after 7 days of age. (31)(32)

Although meningitis is often associated with bacteremia, bacteremia is not always present (Table 2). In a retrospective study of more than 9,000 very-low-birthweight (VLBW) infants, meningitis occurred after 72 hours of age without a positive blood culture in approximately one-third of the 134 VLBW infants who were diagnosed with meningitis. (8) This finding was replicated in a cohort study of 4,632 infants, in which 30% of infants with meningitis had negative blood cultures. (33) Thus, it is appropriate to consider LP in the routine evaluation for LOS (Figure). Failure to diagnose and appropriately treat bacterial and especially fungal meningitis in these cases can lead to substantial morbidity and mortality.

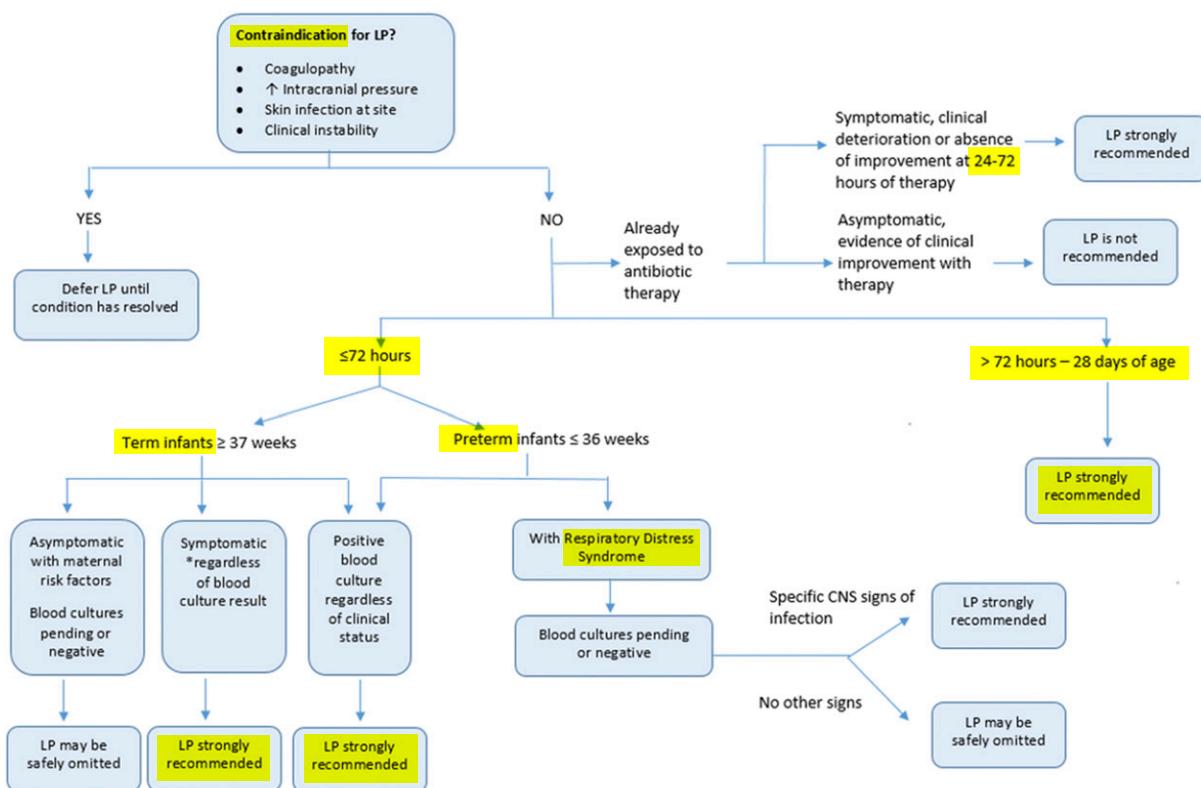


Figure. Algorithm of recommendations on when to perform a lumbar puncture in neonates being evaluated for sepsis. CNS=central nervous system; LP=lumbar puncture. Printed with permission from Elsevier. (56)



## LPs IN OUTPATIENT FEBRILE INFANTS

The risk of contracting meningitis exists beyond the initial newborn hospitalization period. In the outpatient setting, meningitis must be considered when infants **less than 90 days of age** present with **fever** (rectal temperature  $>100.4^{\circ}\text{F}$  [ $38^{\circ}\text{C}$ ]). Most febrile infants in the outpatient setting are ultimately diagnosed with a viral illness; however, 10% to 16% of febrile infants younger than 28 days have growth of a known pathogen in blood, CSF, stool, or urine cultures, known as a serious bacterial infection. (34)(35)

Current practice guidelines recommend that all infants **younger than 28 days** who have a **fever** ( $>100.4^{\circ}\text{F}$  [ $38^{\circ}\text{C}$ ]) should receive a **"complete sepsis evaluation,"** including blood, urine, and CSF cultures and should be admitted for parenteral antibiotic therapy. (36) The Rochester criteria are the only published risk stratification criteria that do not include a routine LP in infants younger than 28 days. (37) In a multicenter validation study of the Rochester criteria, 8 (88%) of 9 infants younger than 28 days eventually diagnosed with meningitis were classified as high risk (LP recommended); however, 1 infant with meningitis would

have been classified as low risk (missed case). (38) The authors suggest using caution in applying the Rochester criteria in febrile infants younger than 28 days, especially when electing not to perform an LP. (38)

Traditionally, risk stratification strategies using the Rochester, Philadelphia, and Boston criteria have been used to supplement history and physical findings in infants 29 to 90 days of age. (37)(39)(40) These guidelines include laboratory and clinical criteria to aid in risk stratification. According to most of these guidelines, low-risk infants of this age may often be treated without LP (Table 3). For high-risk infants who do not have a urinary tract infection, LP and hospitalization with antibiotics are recommended pending culture results. (36)

## RISKS ASSOCIATED WITH LPs

One of the most common reasons for deferring an LP in the neonatal population is perceived **clinical instability**. (8) Pre-term infants undergoing an LP, especially VLBW infants, may deteriorate clinically; recent trials have suggested the

TABLE 2. **Role of Lumbar Punctures in the Evaluation for Late-onset Sepsis**

STUDY	POPULATION	RESULTS
Stoll et al, 2004 (8)	9,641 infants with birthweight of 401–1,500 g who survived at least 72 hours	134/9,641 (1%) infants had culture-positive meningitis after 72 hours of age 45/134 (34%) infants with meningitis did not have a positive blood culture
Schwenski et al, 1991 (32)	114 preterm and term infants $>7$ days of age with an LP	3/114 (3%) infants had culture-positive bacteremia with concomitant meningitis
Visser and Hall, 1980 (21)	193 cultures obtained from 400 infants of 25–42 weeks' gestation, with birthweights of 634–5,650 g, who were evaluated after 72 hours of age	5/21 (24%) cases of late-onset sepsis were associated with meningitis
Tsai et al, 2014 (24)	713 infants with 942 episodes of sepsis occurring after 6 days of age	50/942 (5%) cases of late-onset sepsis had co-existent meningitis
Kaul et al, 2013 (29)	102 infants over 72 hours of age with clinical features of sepsis	23/102 (23%) of infants with late-onset sepsis had meningitis
Ansong et al, 2009 (30)	13,495 infants who underwent at least 1 LP after postnatal day 7	<b>13/24 (54%)</b> of infants with late-onset GBS sepsis also had meningitis
Ajayi and Mokuolu, 1997 (31)	Phase 1: 243 infants with suspected sepsis, and those with risk factors for sepsis who had an LP after 72 hours of age Phase 2: 157 infants with signs of severe sepsis who had an LP after 72 hours of age	32/400 (8%) of infants evaluated for sepsis after 72 hours of age had meningitis
Smith et al, 2008 (33)	4,632 infants $<34$ weeks' gestation who had an LP	95/4,632 (2%) infants had positive cerebrospinal fluid cultures 28/92 (30%) of infants with meningitis with concurrent blood cultures had negative blood cultures

GBS=group B Streptococcus; LP=lumbar puncture.

TABLE 3. **Low-risk Criteria** for Febrile Infants in the Outpatient Setting

	BOSTON (40)	PHILADELPHIA (39)	ROCHESTER (37)
Postnatal age	28–89 d	29–60 d	<60 d
Temperature	>100.4°F (38°C)	>100.7°F (38.2°C)	>100.4°F (38°C)
History (categorized as low risk)	No immunizations in the past 48 h No antibiotics in the past 48 h <b>Not dehydrated</b> Gestational age not specified	No specifications provided	Term infant No perinatal antibiotics Not discharged after mother No underlying disease
Physical examination	Well appearing No evidence of ear, skin, or soft tissue infection	Well appearing with an unremarkable examination result	Well appearing No evidence of ear, skin, or soft tissue infection
Laboratory findings	WBC count <20,000/ $\mu$ L ( $20 \times 10^9$ /L) CSF WBC count <10/ $\mu$ L ( $10 \times 10^9$ /L) Urinalysis <10 WBC/hpf Chest radiograph with no infiltrate	WBC count <15,000/ $\mu$ L ( $15 \times 10^9$ /L) Band to neutrophil ratio <0.2 Urinalysis <10 WBC/hpf CSF WBC count <8/hpf Negative CSF gram stain Chest X-ray with no infiltrate No RBCs or WBCs in stool	WBC count 5,000–15,000/ $\mu$ L ( $5\text{--}15 \times 10^9$ /L) Absolute bands <1,500/ $\mu$ L Urinalysis <10 WBC/hpf Stool WBC count <5/hpf

CSF=cerebrospinal fluid; hpf=high-power field; RBC=red blood cell; WBC=white blood cell.

use of ultrasound guidance to minimize the number of attempts. (41) The National Institute for Health and Care Excellence (NICE) guidelines on bacterial meningitis in childhood recommends delaying an LP when contraindications, such as **cardiorespiratory compromise**, are present, because this may produce further clinical deterioration. However, an LP should be performed once these contraindications have resolved. (42)

After an LP is performed, various bleeding complications, such as spinal hemorrhages and hematomas, have been described; however, reports in infants are limited. (43) **Thrombocytopenia** at the time of the procedure is a risk factor for these complications but there is **no** evidence supporting a particular platelet threshold. (43) The NICE guidelines on the management of blood transfusions recommend **considering prophylactic platelet transfusion to reach a platelet count greater than  $50 \times 10^3/\mu$ L ( $50 \times 10^9$ /L) in patients having invasive procedures.** (44)

Other rare complications associated with LPs include epidermoid spinal tumors and brain herniation. Acquired epidermoid spinal tumors have been described in the literature as occurring because of the introduction of epidermal tissue into the spinal canal when an LP is performed without using a stylet. For this reason, using a needle with the smallest gauge and a stylet is recommended. (45) Transforaminal and transtentorial herniation can occur because of elevated intracranial pressure, but the presence of an

open fontanelle and increased skull compliance makes the incidence of these complications uncommon in infants. (46)

Performing an LP in the presence of a skin infection at the puncture site is not recommended because of the risk of infection spreading to the bone. (47) Although there may be hypothetical concerns that performing an LP in the setting of bacteremia could lead to the subsequent development of meningitis, a retrospective study of 1,089 infants with culture-positive bacteremia suggested that LP-induced meningitis is rare and the risk is clinically insignificant. (48) **In addition, the risk of missing the diagnosis of meningitis is higher than the possibility of developing meningitis from the procedure.** (48)

## DIFFICULTIES IN INTERPRETING LPs

The diagnosis of meningitis can be difficult even when an LP is performed. Complexity surrounding the interpretation of an LP can decrease the benefit of the procedure relative to the risk. For example, infants are often exposed to intrapartum or empiric antibiotics before an LP is performed, which can result in a falsely negative CSF culture in the presence of meningitis. In a study of 128 children with bacterial meningitis, **complete sterilization of meningococcus occurred within 2 hours**, while **sterilization of pneumococcus was beginning to occur by 4 hours into therapy.** (49) In these instances, clinicians rely on CSF parameters, such as glucose, protein count, and WBC and red blood cell (RBC) counts, to

make the diagnosis of meningitis. It has been challenging to develop reference ranges for infant CSF parameters, given that several factors, such as gestational age, postnatal age, and a higher probability of traumatic LPs, are known to alter these parameters. (50)

In a large study of 9,111 term and near-term infants, no specific CSF parameters were identified to exclude meningitis. (51) Meningitis occurred in the presence of normal CSF glucose, protein, and WBC counts, and 38% of infants with culture-positive meningitis had negative blood cultures. (51) Another study of more than 4,600 infants of less than 34 weeks' gestational age found that a combination of all 3 parameters (CSF protein, glucose, and WBC count) provides a more reliable way of "ruling in" meningitis. In this study, an infant who underwent an LP and had CSF values greater than 25 WBC cells/ $\mu$ L, a glucose concentration of less than 10 mg/dL (0.56 mmol/L), and protein level of more than 250 mg/dL (2,500 g/L) had a 164-fold increase in odds of having a positive CSF culture. However, only 18% of infants with positive CSF cultures were identified using these cutoff values. (33) The interpretation of CSF WBC count becomes even more challenging in the setting of a traumatic LP, because the CSF WBC count is affected by the presence of peripheral RBCs. A study of more than 6,000 infants showed that adjustment of the CSF WBC count by either a correction factor or the peripheral RBC-WBC ratio leads to an underestimation of the true number of WBCs in the CSF, masking of true CSF leukocytosis, and missed cases of meningitis. (52)

Given the difficulties that arise in the interpretation of CSF indices for the diagnosis of meningitis when a CSF culture is not available or reliable (ie, postantibiotic exposure), it is ideal to attempt to perform an LP before the initiation of antibiotics when meningitis is suspected, especially in infants who are clinically stable. This improves the reliability of the CSF culture and assists in guiding duration and choice of appropriate antibiotic therapy. In the setting of antibiotic exposure, clinicians should be mindful of the possibility of meningitis even in the presence of sterile CSF cultures. More recently, real-time polymerase chain reaction (PCR) testing is being used for faster detection of multiple pathogens in CSF, including viruses and bacteria. Not only does it have improved sensitivity and specificity, but it also has a higher detection rate compared with traditional culture methods among patients exposed to antibiotics. (53) For these reasons, real-time PCR panels are a promising tool in the diagnosis of meningitis and may improve the diagnostic usefulness of LP in certain situations.

## SUMMARY AND RECOMMENDATIONS

- Meningitis is a devastating infection in infants and is associated with substantial mortality and morbidity, especially in ELBW infants. (1)
- The most reliable way to diagnose meningitis is with CSF analysis that is obtained via an LP; however, approximately 30% to 70% of infants being evaluated for EOS and LOS, respectively, do not undergo an LP. (6)(7)(8)
- In asymptomatic infants who are being evaluated for sepsis because of maternal risk factors and in those whose clinical symptoms are likely secondary to noninfectious causes, the likelihood of meningitis is low. In these cases, it is appropriate to defer an LP. (19)(20)(54)(55)
- Meningitis is common in the setting of bacteremia; therefore, all infants with early-onset or late-onset bacteremia should undergo an LP. (21)(51)
- In the NICU, meningitis is more likely to occur with increasing postnatal age and may also occur in the presence of a negative blood culture. It is appropriate to include an LP in the routine evaluation for LOS. (8)(31)(33)
- In the outpatient setting, all febrile infants younger than 28 days should have a complete sepsis evaluation, which includes an LP. (36) In infants between 29 and 90 days of age, risk stratification criteria should be used to identify high-risk infants who will require an LP. (36)
- Given the difficulty in interpreting CSF indices to diagnose meningitis in the setting of a sterile CSF culture, it is ideal to perform an LP before initiating antibiotics in infants at high risk for meningitis. (49)(50)
- If an LP is performed after antibiotics have been initiated, clinicians should be mindful of the possibility of meningitis even in the presence of a sterile CSF culture.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the maternal, perinatal, and neonatal risk factors for neonatal sepsis.
- Know the causative infectious agents and pathogenesis of early- and late-onset meningitis as well as meningitis associated with ventricular drainage devices.
- Know the clinical manifestations and laboratory features of meningitis and meningoencephalitis.
- Know the management, complications, and outcomes of meningitis and meningoencephalitis.

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1. A preterm infant with birthweight 1,350 g is 4 days old and experiencing increasing respiratory distress and more frequent apnea than in the first few days after birth. A sepsis evaluation is commencing and the team is considering the tests that will be done, including the possibility of performing a lumbar puncture. Which of the following signs and symptoms are more likely to be present in meningitis in infants of less than 2,500 g birthweight compared with larger infants?
  - A. Bulging fontanelle.
  - B. Irritability and increased crying.
  - C. Seizures, both electrographic and clinical.
  - D. Apnea, jaundice, and abdominal distention.
  - E. Fever.
2. An infant is diagnosed with probable sepsis and meningitis after initial laboratory evaluation prompted blood culture and lumbar puncture. Which of the following statements regarding early-onset sepsis and associated meningitis is correct?
  - A. The most common cause of early-onset sepsis and associated meningitis in preterm infants is *Escherichia coli*.
  - B. Group B *Streptococcus* is isolated in 10% of cases of early-onset sepsis and associated meningitis.
  - C. The incidence of early-onset sepsis in the United States is similar to that found in developing countries.
  - D. In settings where intrapartum chemoprophylaxis for group B *Streptococcus* has been implemented, the occurrence of group B *Streptococcus* meningitis has been eliminated.
  - E. Technically, early-onset sepsis and meningitis refers to diagnoses made based on initial cultures obtained in the first hour after delivery.
3. A newborn is noted to have hypoglycemia and irritability 3 hours after delivery. The team is considering further evaluations. According to the 2012 recommendations by the Committee on Fetus and Newborn, in which of the following circumstances is a lumbar puncture suggested?
  - A. Hypoglycemia refractory to initial interventions.
  - B. Infants with clinical course or laboratory data suggestive of sepsis.
  - C. Infants with persistent symptoms despite negative blood culture.
  - D. Maternal risk factors for infection such as chorioamnionitis.
  - E. Fever or hypothermia in the first 12 hours after delivery.
4. An infant born at 28 weeks' gestational age is now 2 weeks old and has increased apnea and feeding intolerance. A blood culture specimen is obtained and antibiotics are started. The team considers also performing a lumbar puncture. Which of the following statements regarding the risk of meningitis in preterm infants is correct?
  - A. Meningitis occurs less commonly in association with late-onset sepsis than early-onset sepsis.
  - B. Meningitis occurs without a positive blood culture in approximately one-third of patients in this population.
  - C. The most common organism isolated from cultures in this circumstance is *Klebsiella*.
  - D. Blood culture or cerebrospinal fluid culture isolating coagulase-negative *Staphylococcus* can be ignored as a contaminant and be considered as negative.
  - E. Invasive candidiasis co-occurs in approximately 50% of infants who have bacterial meningitis.

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5. A lumbar puncture is performed in an infant who has a positive blood culture for *Escherichia coli*. The cerebrospinal fluid specimen is sent for cell count, other laboratory evaluation, and culture. Which of the following statements regarding interpretation of laboratory findings is correct?
- A. Using the 3 parameters of cerebrospinal glucose, protein, and white blood cell count, the diagnosis of meningitis can be both ruled in and ruled out with about 90% accuracy.
  - B. A normal cerebrospinal fluid glucose concentration within 24 to 48 hours after starting antibiotics indicates that there is no possibility of bacterial meningitis.
  - C. The white blood cell count in cerebrospinal fluid is not affected by the presence of peripheral red blood cells.
  - D. Real-time polymerase chain reaction testing of cerebrospinal fluid is not likely to be beneficial because antibiotic treatment will eliminate positive findings in a similar fashion to culture techniques.
  - E. Sterilization of *Pneumococcus* in cerebrospinal fluid begins 4 hours after initiation of antibiotic therapy.

## When to Include a Lumbar Puncture in the Evaluation for Neonatal Sepsis

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# Antibiotic Resistance in the Neonatal Intensive Care Unit

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## Education Gaps

1. Antibiotic-resistant bacteria in the NICU are a major source of morbidity and mortality among infants.
2. The genetic mechanisms of resistance and modes of transmission are not completely understood and continue to evolve rapidly.

## Abstract

Antibiotic-resistant bacteria are an increasing problem in the NICU. Ineffective empiric antibiotic therapy is associated with increased risk for morbidity and mortality. Organisms that are resistant to multiple antimicrobial agents (multidrug-resistant organisms) are particularly problematic. These organisms may be transmitted to infants if infection control practices are not adhered to, or they may be created by antibiotic exposure. Therefore, meticulous infection prevention—including hand hygiene, surveillance cultures, contact precautions, and selective decolonization—and antibiotic stewardship are important strategies to minimize drug resistance in the NICU.

## Objectives After completing this article, readers should be able to:

1. Describe the genetic mechanisms of antibiotic resistance among bacteria as well as the means of transmission of such genetic material among bacteria.
2. Describe the epidemiology of antibiotic-resistant bacteria in the NICU.
3. Understand strategies aimed at preventing ongoing transmission of antibiotic-resistant bacteria in the nursery setting.

**AUTHOR DISCLOSURE** Drs Ramirez and Cantey have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
ESBL	extended-spectrum $\beta$ -lactamase
MDRO	multidrug-resistant organism
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
VRE	vancomycin-resistant <i>Enterococcus</i>

## INTRODUCTION

Bacterial infection is a major cause of morbidity and mortality for infants cared for in the NICU. Late-onset sepsis, or sepsis occurring after age 72 hours, affects

more than 5% of all NICU admissions. (1) Risk for late-onset sepsis increases to more than 25% for infants born with birthweights less than 1,500 g and up to 30% to 40% for infants less than 1,000 g. (2)(3) Antibiotic stewardship and infection prevention strategies can reduce the risk of developing bacterial infection. However, once infection is present, prompt and effective antibiotic therapy is the mainstay of treatment. Unfortunately, widespread antibiotic overuse has increased selective pressure on bacteria and driven the rapid rise of multidrug-resistant organisms (MDROs, Table 1) in NICUs worldwide. (4) Infants with sepsis caused by MDROs are at increased risk for morbidity and mortality, in large part because they are less likely to receive empiric antibiotic therapy with activity against the pathogen. It may be days before antibiotic susceptibilities are available, the extent of the organism's drug resistance is known, and effective antibiotic therapy is initiated.

The Centers for Disease Control and Prevention (CDC) define MDROs as organisms that are resistant to multiple antimicrobial agents. (5) Although some MDROs (eg, methicillin-resistant *Staphylococcus aureus* [MRSA] and vancomycin-resistant *Enterococcus* [VRE]) are named for their resistance to a single agent, they are usually resistant to many antibiotics. The risk for bloodstream infection with an MDRO has increased logarithmically in the last 2 decades. (6) MDRO infections in the nursery setting, in turn, are associated with longer hospitalization, increased costs, and increased risk for mortality. (7)(8) In the developing world,

where antimicrobial agents effective against MDROs are not widely available, antibiotic resistance accounts for more than 100,000 neonatal deaths annually in Asia and sub-Saharan Africa. (9) In this review, we will describe the mechanisms of resistance, clinical management, and prevention strategies for MDROs in the NICU.

## MECHANISMS OF RESISTANCE

Organisms become MDROs by either acquiring resistance genes from other bacteria or by expressing genes on their chromosomes that were previously suppressed. Bacteria can transfer genetic material in various ways, including direct cell-to-cell transfer (conjugation) and uptake of DNA released during cell lysis (transformation). (10) These processes are accelerated when a microbial ecosystem (eg, the microbiome) is exposed to antibiotics, which not only causes bacterial lysis (increasing the pool of available cell-free DNA for transformation) but also places tremendous selective pressure on organisms that carry resistance genes. (11) In addition, some organisms have resistance genes that are stably repressed under normal conditions. When the organism is exposed to an antibiotic, cellular signals stop this repression of resistance genes and allow their expression. The *ampC* gene is an example; it is present but stably repressed on various gram-negative organisms (Table 1) but produces a powerful  $\beta$ -lactamase once expressed, after repeated exposure to  $\beta$ -lactam antibiotics. (12)

TABLE 1. Multidrug-Resistant Organisms and Selected Examples of Resistance Mechanisms

ORGANISM		ENZYME
Gram-positives	Methicillin-resistant <i>Staphylococcus aureus</i>	mecA
	Vancomycin-resistant <i>Enterococcus spp</i>	vanA/vanB <sup>a</sup>
Gram-negatives	Extended-spectrum $\beta$ -lactamase producers	CTX-M
	• Usually via plasmid	SHV
	• SPACE organisms ( <i>Serratia</i> , <i>Pseudomonas</i> , <i>Proteus</i> , <i>Acinetobacter</i> , <i>Citrobacter</i> , <i>Enterobacter</i> ) contain <i>ampC</i> on chromosome	TEM
		OXA
	Carbapenem-resistant <i>Enterobacteriaceae</i> <sup>b</sup>	ampC
		NDM-1
Colistin-resistant gram-negatives		KPC
		IMP
		MCR-1

<sup>a</sup>vanA and vanB have also been identified in vancomycin-resistant strains of *Staphylococcus aureus*.

<sup>b</sup>Note that organisms with extended-spectrum  $\beta$ -lactamase production may acquire the phenotype of carbapenem resistance if they also have efflux pumps or other mutations, even though they lack a carbapenemase resistance gene.

Note that genes that are ubiquitous on the chromosomes of given species can also be exchanged horizontally via mobile genetic elements (including *ampC*, which can be transferred on plasmids to organisms that do not inherently possess *ampC*). As a result, the state of antimicrobial resistance is constantly in flux because of horizontal gene transfer. For example, *vanA* has been transferred from VRE to *S. aureus* isolates, resulting in vancomycin-resistant *S. aureus*. (13)

Once these genes are expressed, they provide antibiotic resistance in various ways. Some, such as *mecA* (which confers  $\beta$ -lactam resistance to MRSA) or *vanA* and *vanB* (which confer vancomycin resistance to VRE), alter the proteins targeted by antibiotics. Others, such as *ampC*, *SHV*, *OXA*, and *bla<sub>NDM-1</sub>*, code for  $\beta$ -lactamases that can directly destroy  $\beta$ -lactam antibiotics. Mutations in efflux pumps can allow bacteria to pump antibiotics out of the cell before reaching their targets. (12)(14)(15) Notably, these resistance elements can complement each other. For example, a gram-negative organism with a genotype that includes efflux pumps and a weak  $\beta$ -lactamase may have a phenotype of a strong extended-spectrum  $\beta$ -lactamase (ESBL) producer, because the efflux pumps lower the level of  $\beta$ -lactam in the cell to the point that even a weak  $\beta$ -lactamase can be very effective. (16)

The broad armamentarium of resistance genes is not surprising. Microorganisms have been combatting each other for millions of years with antibacterial chemicals, long before humans adapted the use of fungal and bacterial proteins for our own uses. Antimicrobial resistance genes have been identified in the fossilized stool (“paleofeces”) of 11th century mummies of persons who died more than 900 years before antibiotics were in clinical use. (17) Bacteria have had millennia to evolve resistance and have the advantage of rapid DNA sharing and cell turnover to allow additional mutation. Professor Severus Snape was discussing the Dark Arts but may as well have been describing MDROs when he said they “are many, varied, ever-changing, and eternal. Fighting them is like fighting a many-headed monster. Which, each time a neck is severed, sprouts a head even fiercer and cleverer than before. You are fighting that which is unfixed. Mutating. Indestructible.” (18)

## EPIDEMIOLOGY AND TRANSMISSION

The prevalence of MDRO colonization and subsequent infection in NICUs has increased sharply over several decades, paralleling other health-care settings. Risk factors for MDRO colonization and infection include prolonged

length of stay, indwelling medical devices, and antibiotic exposure. (5) As a result, intensive care units have a higher burden of MDROs than other inpatient settings, and the NICU is no exception. (19) In the past 5 years, studies in geographically disparate NICUs across the globe have shown consistent increases in both endemic colonization as well as the frequency of outbreaks. (20)(21)(22) MRSA and VRE colonize approximately 4% and 1%, respectively, of infants discharged from NICUs in the United States. (23) Screening for ESBL-producing gram-negative colonization is not commonly performed in nonoutbreak settings, but single-center studies suggest that 10% to 30% of preterm infants are colonized with ESBL-producing organisms during their NICU stay. (20)(24)

There are 3 primary routes for MDROs to enter the NICU: horizontal transmission, vertical transmission, or de novo selection. All 3 mechanisms are discussed herein.

### Horizontal Transfer

Horizontal transfer is defined as the spread of an organism from one patient to another and is one of the primary ways MDROs reach at-risk infants. Transmission can come directly from the hands of health-care workers or visitors, or indirectly from contaminated environmental sources, such as countertops, medical support devices, and stethoscopes. (25)(26) Poor hand hygiene is often the final common pathway by which organisms from any source reach vulnerable infants, making hand hygiene both the most important cause and preventive measure of horizontal transmission. (27) The risk for horizontal transfer depends on various factors, including density of patients, acuity of illness, prevalence of the organism within the unit or hospital, staffing models, and adherence to infection control and prevention practices. (5) The management of endemic or epidemic MDRO transmission, discussed later in this article, focuses on reducing these risk factors.

### Vertical Transfer

Less frequently, MDROs can be transmitted directly from the mother to the infant during labor and delivery or via breastfeeding. The worldwide increase in the prevalence of MDROs includes women of childbearing age, meaning an increasing number of infants are born to women with MDRO colonization. (28) Infants born to women colonized with MRSA or ESBL-producing gram-negatives are at increased risk of becoming colonized with those organisms, and colonization occurs earlier among those infants compared with infants born to mothers who are not colonized. (29)(30) Some proportion of this transfer likely occurs beyond the peripartum period and therefore should be



considered horizontal rather than vertical transmission, but studies have shown that the acquisition can occur in the peripartum period (before age 48 hours). (31) There is a paucity of data regarding the role breastfeeding plays in maternal-to-infant transmission of MDROs. (32) Theoretically, antibiotic exposure via human milk and the intimate skin-to-skin contact could lead to transmission or selective pressure within the infant microbiome; on the other hand, there is evidence that the healthy microbiome established by breastfeeding may be protective against MDRO colonization. (33) Additional research in this area is needed.

#### De novo Selection

Finally, the selective pressure of antibiotic exposure can drive organisms to develop antimicrobial resistance. This can be accomplished either by the exchange of resistance genes among bacteria via plasmids or by the upregulation of previously suppressed genetic information in the bacterial chromosome. (34) These mobile genetic elements are always available to bacteria in microecosystems, but transmission increases sharply when exposed to selective pressure of antibiotics. Fortunately, there is a fitness cost to bacterial carriage of this extra genetic information. (35) If antimicrobial pressures are removed, susceptible wild-type bacteria can outcompete more drug-resistant bacteria and the prevalence of MDROs will decrease. This was shown by de Man et al in a crossover study of 2 NICUs assigned to different antibiotic regimens. (36) NICU A used an antibiotic regimen for late-onset sepsis that included cefotaxime; NICU B used one that included tobramycin. Resistance to cephalosporins was high in unit A but not in B. When the units exchanged antibiotic regimens after 6 months (ie, unit A changed to tobramycin and unit B changed to cefotaxime),

cephalosporin resistance rapidly disappeared from unit A and emerged in unit B. This study illustrates the rapid effect selective antibiotic pressure can have on the NICU environment.

## MANAGEMENT AND PREVENTION

### Screening

Identification of MDRO-colonized infants is a keystone of infection control and prevention in the NICU. In addition to the vital epidemiologic information, screening allows infants to be placed in cohorts to prevent horizontal transmission to other infants and in some cases (eg, MRSA), targeted decolonization therapy. (37)(38) For other pathogens, particularly gram-negative bacteria, screening is less sensitive and therefore less cost-effective. (39) The relative value of screening depends on the number of tests needed to detect one colonized infant, which in turn, is based on the prevalence of a given MDRO in the NICU and in the community, the sensitivity of the test in question, and the frequency with which screening is ordered. (40) Therefore, the optimal screening strategy to detect endemic horizontal transmission will vary among hospitals and among MDROs. During an outbreak, however, the cost-benefit ratio tilts substantially toward frequent, universal screening, and serial surveillance cultures are a key tool during any NICU MDRO outbreak. (5) An example screening regimen is shown in Table 2.

In most cases, colonization with an MDRO is necessary but not sufficient for subsequent sepsis caused by that MDRO. For example, infants colonized with MRSA have a 20-fold increased risk for subsequent MRSA sepsis compared with MRSA-negative infants. (41) However, the first

**TABLE 2. An Example of a Screening Regimen in a Nonoutbreak Clinical Setting**

ORGANISM	SITE	FREQUENCY	MANAGEMENT OF COLONIZED INFANT
MRSA	Nasal <sup>a</sup>	Every 1–2 weeks depending on prevalence	<ul style="list-style-type: none"> <li>• Decolonization with nasal mupirocin and chlorhexidine bathing</li> <li>• Contact precautions until decolonized</li> <li>• Empiric vancomycin in lieu of oxacillin until decolonized</li> </ul>
VRE	Rectal	Every 2–4 weeks or only in outbreak setting depending on prevalence	<ul style="list-style-type: none"> <li>• Contact precautions until discharged<sup>b</sup></li> <li>• Empiric linezolid in lieu of oxacillin until discharged</li> </ul>
ESBL-producing gram-negatives	Rectal		<ul style="list-style-type: none"> <li>• Contact precautions until discharged<sup>b</sup></li> <li>• Empiric meropenem in lieu of gentamicin until discharged</li> </ul>

ESBL=extended-spectrum  $\beta$ -lactamase; MRSA=methicillin-resistant *Staphylococcus aureus*; VRE=vancomycin-resistant *Enterococcus species*.

<sup>a</sup>Nasal swabs are cost-effective. Sensitivity can be increased if other sites are added (eg, axilla, umbilicus, groin).

<sup>b</sup>Decolonization takes months to years; therefore, VRE and ESBL status are an important part of the discharge summary for future clinicians.

sign of MDRO colonization can be a positive clinical culture, especially if the infection is caused by an organism that is screened for infrequently or not at all. (42) A sudden increase in MDROs detected in clinical samples should prompt unit-wide surveillance cultures for the offending pathogen(s), if not already in place.

### Colonized Infants

Once an infant is colonized or infected with an MDRO, several actions should be taken (Table 3). Contact precautions should be initiated, and the infant placed in a separate cohort in a geographically separate area of the NICU. (5) Routine use of gown-and-gloves and meticulous hand hygiene can prevent the spread of MDROs to other infants. In addition, the empiric antibiotic therapy for future sepsis evaluations for that infant should be tailored to match the colonizing MDRO. For example, if the routine practice for late-onset sepsis is to treat empirically with oxacillin and gentamicin, an MRSA-colonized infant should receive vancomycin in lieu of oxacillin. (43) ESBL-colonized infants require empiric meropenem; VRE-colonized infants should receive empiric linezolid. (42)(44) Determining the empiric regimen ahead of time and documenting it in the electronic medical record can prevent incorrect prescribing during future sepsis evaluations. Infants who are MRSA-positive can benefit from targeted decolonization with nasal

mupirocin and chlorhexidine bathing, which has been shown to reduce infections caused by both MRSA and methicillin-susceptible *S aureus*. (37) There has been some preliminary research about using fecal transplants to reduce or eliminate intestinal colonization with VRE or ESBL-producing gram-negative organisms; however, this approach has not been investigated in neonates. Finally, during outbreaks involving infants, the management requires more aggressive infection control processes (Table 3).

### Prevention

The most essential step in preventing horizontal transmission of MDROs in the NICU is proper hand hygiene. (5) Decreased hand hygiene compliance consistently has been linked with MDRO outbreaks in the NICU, and restoring hand hygiene rates before and after patient contact to 100% is a critical step in outbreak control. (21) Hand hygiene is so important that a randomized controlled trial of universal gown-and-glove use showed no additional benefit when hand hygiene compliance was good. (27) Other factors associated with decreased MDRO transmission include avoiding overcrowding and understaffing. Overcrowding refers to excessive number of infants in a given area; the American Academy of Pediatrics recommends a minimum of 120 sq ft per intensive-care bed in multipatient rooms ("bays") and a minimum of 165 sq ft for single-infant rooms. (45)

TABLE 3. **Sample Interventions After Identification of a Multidrug-Resistant Organism Outbreak**

CLASS	INTERVENTION
Hand hygiene	<ul style="list-style-type: none"> <li>• Re-education of all staff</li> <li>• Re-enforcement of existing policy (eg, complex rings, artificial nails)</li> <li>• Hand hygiene audits</li> </ul>
Cohorting	<ul style="list-style-type: none"> <li>• Screening of all infants for offending pathogen</li> <li>• Cohort colonized infants physically</li> <li>• Staff cohorting if possible (eg, nurse cares for only colonized or only noncolonized infants, no crossover)</li> <li>• If cohorting not possible (eg, respiratory therapy or neonatologists) then colonized infants should be seen last</li> </ul>
Staffing and crowding	<ul style="list-style-type: none"> <li>• Create additional floor space if possible</li> <li>• Minimize patient-to-nurse ratio</li> <li>• Minimize number of providers at bedside/inside patient room</li> </ul>
Environment	<ul style="list-style-type: none"> <li>• Re-education of environmental services</li> <li>• Audits of environmental cleaning</li> <li>• Prevent equipment from entering patient room if possible (eg, computer-on-wheels, ophthalmoscopes) and ensure adequate cleaning of all equipment before and after use</li> </ul>
Communication	<ul style="list-style-type: none"> <li>• Prompt formation of multidisciplinary team, including administration and infection control and prevention</li> <li>• Timely communication among multidisciplinary team</li> <li>• Timely communication with parents of infants</li> </ul>

Understaffing (eg, elevated patient-to-nurse ratios) has been associated with increased risk for MDRO transmission. (21)(45)(46) Increased patient volume and acuity in the setting of decreased work space is a combination that reduces attention to hand hygiene and lowers the margin for error. Physical space and staffing concerns require support from administration to alleviate the problem, highlighting the importance of effective communication among the NICU, infection control and prevention, and hospital leadership.

As discussed herein, routine surveillance cultures can help prevent horizontal transmission by adding another layer of personal protective equipment between colonized infants and their clinicians as well as by raising awareness of hand hygiene. Surveillance also allows preemptive decolonization therapy, reducing the overall burden of MDROs in the unit and thereby decreasing opportunities for transmission. It is challenging to directly assess the effectiveness of routine surveillance and subsequent contact precautions because of the wide variety of screening approaches used by various centers. (47) There is some evidence suggesting that contact precautions do have negative unintended consequences, including less patient contact. (48) However, contact precautions are inexpensive and low-risk, and are recommended by the Centers for Disease Control and Prevention (CDC) as an important preventive measure against MDRO transmission. (5)

Finally, an effective antibiotic stewardship program in the NICU is of paramount importance to prevent the emergence of resistant organisms. A full review of antibiotic stewardship in the NICU setting is beyond the scope of this article, but elements of successful programs include audit and feedback of antimicrobial prescribing, a NICU “champion” working in tandem with an antibiotic stewardship program led by pharmacists and infectious disease specialists, ongoing education, sepsis guidelines, and, most importantly, continued reassessment and interventions. (49) Antibiotic stewardship in the NICU can be performed safely and effectively and is critical in preventing de novo selection for MDROs by the inappropriate prescribing of broad-spectrum antibiotics. (50)

Finally, it is important to note that ongoing introduction of MDROs into the NICU will happen. Any given NICU is surrounded by MDROs circulating in the community and in the rest of the inpatient facility; the occasional introduction of MDROs by health-care workers, family or other visitors, or out-born infants transferred from a referring facility is inevitable. The focus of NICU personnel must not be to exist in a sterile bubble, which is an unachievable goal. Instead, they should strive to maintain high rates of hand hygiene, have a system of prospective screening, perform effective

antibiotic stewardship, and ensure that the NICU environment is not overcrowded or understaffed. If these 4 goals can be met, then horizontal transmission can be prevented.

## CONCLUSION

Antibiotic-resistant bacteria in the NICU are an increasing threat to the well-being of our smallest and most vulnerable infants. Resistant bacteria can be introduced from the community or created de novo by selective antibiotic pressure. Agents such as MRSA, VRE, and ESBL-producing gram-negative organisms have been joined more recently by vancomycin-resistant *S aureus*, carbapenem-resistant gram-negatives, and other organisms for which we have limited treatment options. Targeted decolonization has some efficacy against MRSA colonization, but fecal carriage of VRE and ESBL producers is difficult to mitigate. Routine surveillance cultures, effective antibiotic stewardship, and meticulous hand hygiene remain the best weapons we have to combat antibiotic resistance in the NICU.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effective techniques for control of health-care-associated infection in the nursery, NICU, and obstetrical unit.
- Know the pathogenesis and prevention of transmission of infections with multidrug-resistant bacteria.
- Know the management, including understanding of antibiotic resistance, and complications of neonatal infection with *Staphylococcus aureus* and *Staphylococcus epidermidis*.
- Know the epidemiology, prevention, and pathogenesis of neonatal infections with *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Citrobacter*, *Salmonella*, and *Pseudomonas*.

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1. Bacterial infections are a major cause of mortality and morbidity in the NICU. Late-onset sepsis affects more than 5% of all neonates admitted to the NICU and this risk increases with increasing prematurity. What is the rate of late-onset sepsis in extremely low-birthweight infants (<1,000 g birthweight)?
  - A. 5%-10%.
  - B. 10%-20%.
  - C. 20%-25%.
  - D. 30%-40%.
  - E. 45%.
2. Infections resulting from multidrug-resistant organisms (MDROs) have increased exponentially over the past 2 decades and are associated with increased length of hospital stay, increased cost, and increased mortality. Which of the following statements regarding mechanisms of resistance is FALSE?
  - A. Bacteria can transfer resistance genes by direct cell-to-cell transfer (conjugation).
  - B. Antibiotic exposure accelerates the acquisition of resistance genes by causing bacterial lysis thereby facilitating transformation.
  - C. *mecA* is an example of a resistance gene coding for  $\beta$ -lactamase.
  - D. Antibiotic exposure can lead to the expression of resistance gene *ampC* that is stably repressed under normal conditions in some gram-negative organisms.
  - E. Mutations in efflux pumps allow organisms to pump antibiotics out of the cell before they can reach their targets.
3. Intensive care units including the NICU have a higher burden of MDROs because of prolonged length of stay, use of indwelling medical devices, and antibiotic exposure. Which of the following statements regarding MDROs occurrence in the NICU is CORRECT?
  - A. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization affects 10% of infants discharged from NICUs in the United States.
  - B. Poor hand hygiene represents both the most important cause and preventive measure of vertical transfer of MDROs.
  - C. Horizontal transfer during labor or breastfeeding is the primary mechanism of MDRO transmission to at-risk infants.
  - D. Selective antibiotic pressure leads to the slow development of antimicrobial resistance.
  - E. Wild-type bacteria can outcompete drug-resistant bacteria once antimicrobial pressure is removed.
4. Screening and identification of infants colonized by MDROs is a critical step for infection control and prevention. Which of the following statements regarding the implementation of strategies to decrease horizontal transfer is FALSE?
  - A. Contact precautions should be maintained for vancomycin-resistant *Enterococcus* (VRE) and extended-spectrum  $\beta$ -lactamase (ESBL)-producing organisms until NICU discharge.
  - B. Empiric antibiotic therapy for infants colonized with ESBL organisms should be meropenem.
  - C. Nasal swabs are cost-effective for VRE species screening.
  - D. MRSA screening every 1 to 2 weeks depending on prevalence is recommended.
  - E. Screening for gram-negative organisms is less sensitive than screening for MRSA.

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5. During an MDRO outbreak, the management of colonized infants requires more aggressive infection control processes. Which of the following statements regarding recommended steps to control an MDRO outbreak is CORRECT?
- A. Screening of all staff for the offending pathogen is recommended.
  - B. Rectal swab screening of all patients admitted to the NICU is recommended during an outbreak secondary to ESBL-producing gram-negative organisms.
  - C. During a VRE outbreak, weekly nasal swabs are recommended for surveillance.
  - D. Targeted decolonization of staff colonized with MRSA is indicated.
  - E. Contact precautions are not recommended because of the negative unintended consequences, including less patient contact.

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# Challenging the “Culture” of the Tracheal Aspirate

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## Education Gaps

The tracheal aspirate (TA) culture is commonly ordered in the NICU, but clinicians may be less aware of its low sensitivity and specificity. Practices vary—TA culture is used routinely in some units which is costly and unnecessary, whereas other units do not perform TA cultures at all. Inflammatory markers and TA growth may not be due to pneumonia or culture-negative sepsis, and overinterpretation can lead to antibiotic overuse. Clinicians should practice caution and not overdiagnose congenital pneumonia. Given few guidelines on utilization of respiratory cultures in the NICU, clinicians may seek guidance to identify a subset of patients that may benefit from TA.

## Abstract

The tracheal aspirate (TA) culture is commonly ordered in the NICU, but it has low sensitivity and specificity, limited by contamination. Interpretation of a TA culture out of context can lead to antibiotic overuse, which should be avoided. Clinicians should practice caution in the diagnosis of congenital pneumonia and use newer, published approaches to the diagnosis of ventilator-associated pneumonia in neonates. A subset of neonatal patients with risk factors of maternal fever or chorioamnionitis requiring intubation may benefit from TA culture performed within 12 hours after birth, to help identify an organism when blood culture may be negative, and tailor antimicrobial therapies. The more invasive, but more sensitive, technique of nonbronchoscopic bronchoalveolar lavage should be considered in older infants when bacterial isolation from the lower respiratory tract is necessary, because TA culture cannot distinguish between colonization and infection in that population.

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### ABBREVIATIONS

BAL	bronchoalveolar lavage
BPD	bronchopulmonary dysplasia
ETT	endotracheal tube
NB-BAL	nonbronchoscopic bronchoalveolar lavage
TA	tracheal aspirate
VAP	ventilator-associated pneumonia

## Objectives After completing this article, readers should be able to:

1. Describe the limitations of the tracheal aspirate culture, a commonly ordered test in the NICU.
2. Recognize and explain the natural course of airway colonization and the difficulty in distinguishing colonization from infection.
3. Identify which subset of neonates may benefit from having a TA culture.

## INTRODUCTION

Tracheal aspirate (TA) cultures have been historically used in the clinical diagnosis of neonatal pulmonary infections and as an investigative tool in perinatal microbiology research. The endotracheal culture, however, is not a sufficiently reliable sample of the lower respiratory tract secondary to multiple sources of cross-contamination. In the NICU, a TA culture is typically performed in the diagnostic evaluation of an intubated neonate to interrogate for perinatal bacterial exposure, or in an older infant with bronchopulmonary dysplasia (BPD) to assess for ventilator-associated pneumonia (VAP). Culture growth, bacteria on Gram stain, or presence of leukocytes may be variously interpreted as a “positive” TA culture and affect treatment decisions. Reviewing the limitations of neonatal respiratory cultures, however, reveals inadequacies in the diagnosis of congenital pneumonia and VAP in infants. In this review, we will discuss the many challenges constraining the usefulness of this test in our neonatal practice.

## TECHNIQUE OF TA CULTURE TO DIAGNOSE LOWER RESPIRATORY INFECTION

Bacterial infection is clearly a serious threat to neonatal survival, and reliable diagnostic evaluation is critical in the care of infants. Blood cultures are highly sensitive, safe, and relatively uncomplicated to perform in neonates undergoing venipuncture or intravascular line placement when appropriately collected. Respiratory cultures, in contrast, are fraught with challenges, including access to the lower respiratory tract and contamination from oral flora, and bacterial colonization of the endotracheal tube (ETT) itself. (1)(2) The role of the ETT itself in establishing a colonization of bacterial population blurs the relationship between a positive culture from that site and any infectious process. (1)

Aspiration of tracheal secretions from an ETT in a neonate is generally safe, tolerated, and reproducible, but it is not the rapid, sensitive, or specific diagnostic test that clinicians might wish for. Contamination from the upper airway and oropharynx is a major limitation of this type of respiratory culture, resulting in low sensitivity and specificity for bacterial growth. (1)(2)(3)(4) Presence of white blood cells on TA has also been shown to have low sensitivity (67%) and specificity (54%) for infection, even in the presence of pathogenic bacterial growth. (4) Despite these limitations, TA cultures are obtained in the NICU because they are well tolerated and easier to perform compared with other techniques to obtain lower respiratory secretions.

Reliance on TA culture bacterial growth may be associated with prolonged antibiotic treatment, which has been associated with significant downstream morbidities. A central challenge lies in the interpretation of TA results, because the value of the TA culture in the neonatal population is not certain. The Centers for Disease Control and Prevention (CDC) have defined imaging, clinical, and laboratory criteria for VAP in all patients, with microbiological thresholds for bronchoscopic and nonbronchoscopic techniques (including TA) of obtaining respiratory culture specimens. Recently, the CDC included alternative criteria for infants less than or equal to 1 year of age based on imaging findings and signs and symptoms, not requiring microbiological culture (Table). (5)

These criteria may be applicable to ventilator-dependent infants with chronic BPD in the NICU. However, it is unclear whether neonatal clinicians should extrapolate pneumonia guidelines to newborns who undergo intubation after birth. The lack of objective criteria when considering congenital infection and length of antimicrobial treatment leaves the clinician seeking other clinical decision tools.

Many studies have alluded to the helpfulness of the early TA culture and have recommended its use. (4)(6)(7) Our group reported in 2009 on the incidence of TA culture growth in 139 intubated patients of all gestational ages (admitted between August 2006 and January 2007) in whom a TA specimen was obtained within 12 hours of birth, and found the incidence of pathogenic growth was 6.5% in that population. (4) Maternal fever and chorioamnionitis had significantly increased relative risk (6.4,  $P < .02$ ) of pathogenic TA culture growth. (4) Our group concluded that these findings supported the usefulness of obtaining TAs in the immediate newborn period in all neonates. (4)

Ongoing concern regarding antibiotics overuse, coupled with the diagnostic limitations of neonatal TA, seems to call for reanalysis of the usefulness of TA cultures.

## ALTERNATIVE TECHNIQUES TO DIAGNOSE LOWER RESPIRATORY INFECTION

The gold standard for bacterial isolation to diagnose pneumonia is tissue culture, obtained via biopsy or lung puncture, but these are not often considered in the population of critically ill infants. In children, lung puncture has been described as a safe procedure that yields valid information. (8)(9)(10) Both the Klein and Finland studies reported how the lung puncture is the most accurate means of differentiating true lower respiratory infection from upper airway

TABLE. CDC Diagnostic Guideline for Pneumonia

**CDC ALGORITHM FOR CLINICALLY DEFINED PNEUMONIA IN INFANTS  $\leq 1$  YEAR OLD (5)**

Imaging	<p><math>\geq 2</math> serial chest imaging test results with at least <b>1</b> of the following:</p> <p>New and persistent</p> <p>or</p> <p>Progressive and persistent</p> <ul style="list-style-type: none"> <li>• Infiltrate</li> <li>• Consolidation</li> <li>• Cavitation</li> <li>• Pneumatoceles, in infants <math>\leq 1</math> year old</li> </ul> <p><b>Note:</b> In patients <b>without</b> underlying pulmonary or cardiac disease (eg, respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), 1 definitive imaging result is acceptable.</p> <p>AND</p>
Signs and symptoms, specific for infants $< 1$ year old	<p>Worsening gas exchange (for example: 2 desaturations, increased oxygen requirements, or increased ventilator demand)</p> <p>And at least <b>3</b> of the following:</p> <ul style="list-style-type: none"> <li>• Temperature instability</li> <li>• Leukopenia (<math>\leq 4000</math> WBC/<math>\mu</math>L [<math>4 \times 10^9</math>/L]) or leukocytosis (<math>&gt; 15,000</math> WBC/<math>\mu</math>L [<math>15 \times 10^9</math>/L]) and left shift (<math>&gt; 10\%</math> band forms)</li> <li>• New onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements</li> <li>• Apnea, tachypnea, nasal flaring with retraction of chest wall or nasal flaring with grunting</li> <li>• Wheezing, rales, or rhonchi</li> <li>• Cough</li> <li>• Bradycardia (<math>&lt; 100</math> beats/min) or tachycardia (<math>&gt; 170</math> beats/min)</li> </ul>

**CDC ALGORITHM FOR PNEUMONIA WITH COMMON BACTERIAL PATHOGENS AND SPECIFIC LABORATORY FINDINGS (ALL PATIENTS) (5)**

Imaging	<p>Two or more serial chest imaging test results with at least <b>1</b> of the following:</p> <p>New and persistent</p> <p>or</p> <p>Progressive and persistent</p> <ul style="list-style-type: none"> <li>• Infiltrate</li> <li>• Consolidation</li> <li>• Cavitation</li> <li>• Pneumatoceles, in infants <math>\leq 1</math> year old</li> </ul> <p><b>Note:</b> In patients <b>without</b> underlying pulmonary or cardiac disease (for example: respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive imaging result is acceptable</p> <p>AND</p>
Signs and symptoms	<p>At least <b>1</b> of the following:</p> <ul style="list-style-type: none"> <li>• Fever (<math>&gt; 38.0^\circ\text{C}</math> or <math>&gt; 100.4^\circ\text{F}</math>)</li> <li>• Leukopenia (<math>\leq 4,000</math> WBC/<math>\mu</math>L [<math>4 \times 10^9</math>/L]) or leukocytosis (<math>&gt; 12,000</math> WBC/<math>\mu</math>L [<math>12 \times 10^9</math>/L])</li> <li>• For adults <math>&gt; 70</math> years old, altered mental status with no other recognized cause</li> </ul> <p>And at least <b>1</b> of the following:</p> <ul style="list-style-type: none"> <li>• New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements</li> <li>• New onset or worsening cough, or dyspnea or tachypnea</li> <li>• Rales or bronchial breath sounds</li> <li>• Worsening gas exchange (for example: <math>\text{O}_2</math> desaturations [for example: <math>\text{PaO}_2/\text{FiO}_2 &lt; 240</math>], increased oxygen requirements, or increased ventilator demand)</li> </ul> <p>AND</p>

Continued



TABLE. (Continued)

**CDC ALGORITHM FOR PNEUMONIA WITH COMMON BACTERIAL PATHOGENS AND SPECIFIC LABORATORY FINDINGS (ALL PATIENTS) (5)**

Laboratory evidence	At least <b>1</b> of the following: <ul style="list-style-type: none"> <li>• Organism identified from blood</li> <li>• Organism identified from pleural fluid</li> <li>• Positive quantitative culture or corresponding semiquantitative culture result from minimally contaminated LRT specimen (specifically, BAL, PSB, or endotracheal aspirate) – see thresholds below</li> <li>• ≥5% BAL-obtained cells contain intracellular bacteria on direct microscopic examination (eg, Gram stain)</li> <li>• Positive quantitative culture or corresponding semiquantitative culture result of lung tissue</li> <li>• Histopathologic examination shows at least <b>1</b> of the following evidences of pneumonia: <ul style="list-style-type: none"> <li>o Abscess formation or foci of consolidation with intense PMNL accumulation in bronchioles and alveoli</li> <li>o Evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae</li> </ul> </li> </ul>
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**THRESHOLD VALUES FOR CULTURED SPECIMENS USED IN THE DIAGNOSIS OF PNEUMONIA (5)**

SPECIMEN TECHNIQUE	VALUE
Lung tissue	≥10 <sup>4</sup> CFU/g tissue
Bronchoscopically obtained techniques	
BAL	≥10 <sup>4</sup> CFU/mL
Protected BAL	≥10 <sup>4</sup> CFU/mL
Protected specimen brushing	≥10 <sup>3</sup> CFU/mL
NB obtained (blind) specimens	
NB-BAL	≥10 <sup>4</sup> CFU/mL
NB-PSB	≥10 <sup>3</sup> CFU/mL
Endotracheal aspirate	≥10 <sup>5</sup> CFU/mL

BAL=bronchoalveolar lavage; CDC=Centers for Disease Control and Prevention; CFU=colony-forming unit; LRT=lower respiratory tract; NB=nonbronchoscopically; PMNL=polymorphonuclear leukocyte; PSB= protected specimen brush; WBC=white blood cell.

colonization. (9)(10) However, lung puncture has become a procedure of past neonatal practice, because of the uncertain risk versus benefit balance. Bronchoscopic methods of obtaining respiratory samples, common in adults, including bronchoalveolar lavage (BAL) or protected specimen brush, have not been well developed in neonatal populations.

Nonbronchoscopic BAL (NB-BAL) has emerged as a more feasible method of obtaining lower respiratory samples in infants. The NB-BAL technique involves advancing a suction catheter deep into the lower airways until resistance is met, and performing saline lavage to collect the sample; this approach can also be referred to as a blind BAL. (11) Dell'Orto et al published descriptions of cell counts in a NICU population which included 276 infants who underwent NB-BAL, 36 of which were determined to have congenital pneumonia or VAP. (12) Sensitivity, specificity, and effect of duration of assisted ventilation were determined. (12) Neutrophil count had moderate reliability for pneumonia. (12) NB-BAL using a specific catheter was successfully

used without complications in a large, observational, prospective study of 198 newborns to study the rate of neonatal VAP. (13) NB-BAL, however, has not been adopted in most neonatal practices as the routine respiratory culture technique over TA culture, but appears to be feasible and tolerated, especially in older infants. (11)

**NATURAL COURSE OF AIRWAY COLONIZATION**

Investigators have attempted to describe bacterial colonization trends of an ETT of an intubated neonate. Studies have demonstrated that an increasing percentage of intubated neonates will have bacterial growth on TA cultures because of airway colonization over time. (4)(14)(15) When TA culture specimens were obtained in infants less than 12 hours old, more than 85% to 90% of these culture specimens were sterile. (4)(15) Slagle et al described a pattern of progression of colonization from sterile endotracheal TA cultures to isolation of gram-positive bacteria, then later

isolation of gram-negative bacteria. (15) A small 1980 study by Brook et al found that TA cultures done on infants in the first 5 days of intubation largely grew bacteria regarded as nonpathogenic, presumably from oropharyngeal contamination, but 2 of 38 infants were clinically diagnosed as having pneumonia and had correlation of their TA and blood culture growth. (6)

Cordero et al described an evolving microbiome of the neonatal trachea by obtaining serial TA cultures, and found 40% of intubated infants were colonized by gram-positive cocci by 7 days after birth, and gram-negative rod colonization steadily increased to approximately 40% by 7 weeks after birth. (14) Growth of gram-negative rods was usually concurrent with that of gram-positive cocci. Biofilms are then thought to support persistent colonization, as bacteria continue to be protected in a matrix of polymeric substance, and are the major barrier to eradication efforts. (1)(16) Purulence (defined as presence of more than 24 polymorphonuclear cells per high-power field) was also common, with children receiving long-term ventilation showing no other signs of pneumonia, thus challenging the assumption that purulent secretions are equivocal to infection. (17)

Standard culture methods may fail to identify all potentially harmful microbes, because facultative and anaerobic bacteria can evade detection. *Ureaplasma* and *Mycoplasma* species have been implicated in the pathogenesis of preterm labor and severe BPD. (18)(19)(20) The reported incidence of *Ureaplasma* colonization of respiratory tracts of preterm infants is as high as 33% in very-low-birthweight infants and inversely related to gestational age. (18) Interestingly, infants colonized with *Ureaplasma* species appear to show less severe respiratory distress syndrome but are more likely to have early emphysematous changes that evolve into BPD. However, the difficulty in isolating *Ureaplasma* and *Mycoplasma* species using standard culture methods limits our detection of such colonization or infection. In addition, macrolide treatment has not been shown to be successful for eradicating, or protecting against, the development of BPD. (19)

## CONGENITAL PNEUMONIA

Congenital pneumonia is a challenging diagnosis, because newborn infants often have respiratory distress or inflammatory markers related to alternative pathologies, such as respiratory distress syndrome, meconium aspiration syndrome, or early barotrauma. (21) Bacteria found in the tracheal secretions in a newborn in close proximity to birth may have aspirated a maternal source during the birth process or the bacteria may be prenatally acquired. The

epidemiology of neonatal pneumonia depends on the clinical setting and population where the infant is born. (21) Studies by Brook et al and Sherman et al concluded that TA cultures were helpful in neonates for the diagnosis of congenital pneumonia and recommended their use. (6) (7) Goldman challenged their interpretation of positive TA cultures in the diagnosis of congenital pneumonia, because in these studies, TA cultures were not correlated with radiographic findings or tissue culture. (22) Goldman proposed that TA culture growth in earlier studies was associated with congenital colonization, not necessarily congenital pneumonia. (22)

TA growth may correlate with maternal intrauterine infection, but the neonate may or may not have congenital pneumonia. (21) Asphyxia in the setting of infection can lead to aspiration of infected amniotic fluid. (21) Young et al showed that the incidence of positive TA cultures was greater in neonates exposed to chorioamnionitis, but it is not clear whether all these infants had clinical features of congenital pneumonia. (23) Alternatively, Dell'Orto et al showed that NB-BAL neutrophil counts correlated with the clinical diagnosis of pneumonia but not chorioamnionitis. (12)

When TA specimens were obtained from all neonates within 12 hours of birth, close to 90% were sterile, supporting the fact that the test is not necessary in all intubated infants. (14)(15) In the other 10% of infants who showed bacterial growth, the question remains whether the positive TA culture is more helpful or more misleading. A TA culture does provide a second culture specimen, and may result in pathogenic growth even when the blood culture is negative, suppressed secondary to maternal antibiotic pretreatment. (4)

In the study by Booth et al, among the 6.5% of neonates with pathogenic TA growth (all obtained within 12 hours of birth), antibiotic pretreatment of the mother or infant was found in 89%, presumably because of the slower rise of antibiotic concentration in lung tissue compared with serum. (4) Thus, identification of a causative organism may come from the TA specimen alone, and allow antibiotic therapies to be tailored. Neonates with the highest relative risk of pathogenic bacterial growth were those born to women with a fever or chorioamnionitis. (4) Given the challenges of drug resistance, identification of species and sensitivities is clinically relevant for some infants. However, one should consider the low case incidence and importance of clinical correlation.

## VENTILATOR-ASSOCIATED PNEUMONIA

VAP is a severe complication of mechanical ventilation that can occur in the NICU; however, the true incidence in

neonates and definitions and recommendations have been lacking in the neonatal population. The CDC defines VAP for infants younger than 1 year, but many of these criteria are observer dependent and are not specific to neonates (Table). (5) Nosocomial infections are a major threat to infant survival, so during an acute deterioration it is important to consider VAP in infants receiving long-term ventilation. Intensive care unit patients are at increased risk of acquiring dangerous nosocomial infections because of frequent invasive procedures, medical hardware and devices necessary for intensive care, and concentrated exposure to potentially drug-resistant organisms. (3) Advances in respiratory technology and efforts for rapid extubation of infants have likely decreased VAP rates in neonates. (11)

Cernada et al reviewed the numerous challenges in the diagnosis and treatment of VAP in neonates, outlined prevention strategies, and proposed a new diagnostic approach to neonatal VAP, with a useful flow diagram. (11) The NB-BAL (with a specific blind-protected catheter) appears to be the most reliable and safe method in a neonate suspected of having VAP, meeting CDC clinical and radiographic criteria. (11) The NB-BAL allows for less contamination and higher sensitivity and specificity, closer to that of the invasive BAL. Cernada et al emphasize the need for a trial to compare the NB-BAL to the traditional TA culture approach in neonates. (11)

## BRONCHOPULMONARY DYSPLASIA

Prenatal exposure to bacteria may lead to accelerated lung maturation initially, but ultimately may lead to worsening chronic lung disease. (24)(25) There is an association between histologic chorioamnionitis and improved initial respiratory course, suggesting a protective effect for some against severe respiratory distress syndrome. (24)(26) However, a subset of these neonates exposed to chorioamnionitis demonstrate significant respiratory decline, suggestive of a lingering inflammatory reaction, which is likely amplified by the effects of mechanical ventilation. (25) These infants have persistent oxygen or pressure needs and ultimately develop BPD. This clinical pattern aligns with investigations that have shown an association between markers of antenatal infection and increased risk of BPD, with many studies specifically implicating gram-negative bacteria. (27)

In older infants, pulmonary infections can worsen BPD or result in decompensation and death. Antibiotic eradication efforts are not successful in this patient population, secondary to the presence of endotracheal biofilms. (16) The “late” TA culture may yield information about the specific bacteria colonizing the airways of infants with BPD, which

might guide medication choice if antimicrobial drugs are clinically indicated. (23) However, the TA culture alone should not be used without clinical context for the determination of infection in the setting of BPD; NB-BAL may be a better alternative to more accurately assess for lower respiratory tract infection. (11) The uncertainty associated with information from TA culture strongly suggests cautious regard for the results and interpretation only in the context of all the clinical information available.

## PROPOSED RECOMMENDATIONS

Based on the reviewed studies, we recommend refraining from the practice of routine TA cultures in all intubated neonates. Because neonatal clinicians may feel compelled to overtreat a “positive” TA culture result, we recommend consideration *only* in the immediate newborn period *and* in the context of specific risk factors. TA cultures should not be pursued in neonates born with noninfectious maternal indications, even if they require intubation for respiratory distress syndrome. Early antibiotic exposure can contribute to morbidities and antimicrobial resistance, and antibiotic overuse should be avoided. (28) Diagnosis of congenital pneumonia (or culture-negative sepsis) requires careful consideration, and antibiotics should not be prolonged without weighing the risks and benefits of therapies, and reliability of objective data.

Obtaining a TA specimen may be considered in a subset of neonates with specific risk factors of maternal fever or chorioamnionitis, who require intubation within 12 hours of delivery, if there is a high index of suspicion for infection. It would also be acceptable to avoid obtaining any TA specimen, even in this elevated risk group, because of the limitations reviewed. However, a secondary culture site in this subset of neonates may be useful in the rare detection of a pathogen not identified on serum testing, or more commonly, assist clinicians in ruling out infection, thus decreasing antibiotic overtreatment of mild inflammation.

Interpretation of any TA culture growth must be contextual, considering biomarkers of inflammation, clinical signs of pneumonia, and radiographic findings. A “positive” TA culture alone should not be translated as congenital pneumonia. Because of the inability to distinguish infection from colonization and poor correlation with blood cultures in older infants, we propose that TA culture specimens should not be obtained in intubated infants older than 12 hours. If the diagnosis of VAP is highly suspected in an older infant receiving ventilation, clinicians should consider following CDC criteria for clinically defined VAP (Table). Alternatively, if bacterial isolation is deemed to be necessary, clinicians

should use the most recently published diagnostic approach using NB-BAL (11) and reference values and thresholds (5) (12) rather than obtaining a traditional TA specimen.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathogenesis and causative agents in an infant in whom neonatal pneumonia is suspected.
- Know the clinical, imaging, and laboratory features and plan the management of an infant in whom neonatal pneumonia is suspected.

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## Challenging the "Culture" of the Tracheal Aspirate

Colleen C. Claassen and William J. Keenan

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# Index of Suspicion in the Nursery

## 1 A Neonate with Severe Pallor

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### ANTENATAL AND BIRTH DETAILS

A female infant is born to a 28-year-old, gravida 2 woman in a nonconsanguineous marriage. The mother had a history of 1 prior miscarriage at 3 months of gestation. The antenatal period during this current pregnancy had been uneventful. The infant is delivered at 37 completed weeks of gestation via emergency cesarean section in view of decreased fetal movements and nonreassuring fetal heart tracings. There is no history of bleeding per vaginum before delivery and the amniotic fluid is clear at the time of delivery. The neonate cries immediately after birth and has Apgar scores of 7, 8, and 9 at 1, 5, and 10 minutes after birth, respectively. The placenta weighs 410 g and is normal on gross examination without any retroplacental clots. There is no family history of recurrent blood transfusions, leg ulcers, gallstones, or abdominal surgeries.

### PRESENTATION

Immediately after birth, the infant is noted to have severe pallor and respiratory distress. She is transferred to the NICU, and mechanical ventilation is started in view of the severe respiratory distress. At the time of admission, the infant has a heart rate of 178 beats/min, respiratory rate of 70 breaths/min, temperature of 97.7°F (36.5°C), oxygen saturation of 88% on respiratory support with labiality, and blood pressure of 86/50 (mean 62) mm Hg. On examination, the infant's weight, length, and head circumference are 2,860 g (52nd percentile), 48 cm (57th percentile), and 33 cm (52nd percentile), respectively. The infant has severe pallor, but no cyanosis, icterus, edema, or facial dysmorphism; skin lesions; limb abnormalities; or genital abnormalities. Respiratory distress presents as tachypnea, retractions, and nasal flaring. Cardiovascular examination reveals loud second heart sound with a soft systolic murmur and hyperdynamic precordium. On abdominal examination, the liver is palpable 2 cm below the costal margin and the spleen is not palpable.

### EVALUATION

On evaluation, the infant has a hemoglobin concentration of 4.2 g/dL (42 g/L) and packed cell volume of 14%. Both the mother and neonate are blood group O positive; the infant's platelet count is  $1.9 \times 10^3/\mu\text{L}$  ( $1.9 \times 10^9/\mu\text{L}$ ) and white blood cell (WBC) count is  $23,100/\mu\text{L}$  ( $23 \times 10^9/\text{L}$ ; corrected WBC  $15,930/\mu\text{L}$  [ $15.9 \times 10^9/\text{L}$ ]) with 56% polymorphonuclear leukocytes, 38% lymphocytes, and 4% monocytes. Peripheral smear shows anisopoikilocytosis with macrocytes, tear drop cells, schistocytes, and polychromia with abundance of nucleated red blood cells and a reticulocyte count of 20%. Direct Coombs test result is negative. Sepsis

**AUTHOR DISCLOSURE** Drs Dargu, Kallem, Patil, Subramanian, and Murki have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

screen is normal and blood culture shows no growth of organism. Liver function test shows a total bilirubin of 1.3 mg/dL (22.2  $\mu$ mol/L), aspartate aminotransferase 64 U/L (1.07  $\mu$ kat/L), alanine aminotransferase 24 U/L (0.4  $\mu$ kat/L), total protein 5 g/dL (50 g/L), and albumin 2.9 g/dL (29 g/L). Arterial blood gas at the time of admission shows a pH of 7.37,  $P_{CO_2}$  10.3 mm Hg (1.37 kPa),  $P_{aO_2}$  206 mm Hg (27.4 kPa), and base excess -19.8 mmol/L. Two-dimensional echocardiography performed 4 hours after birth reveals dilated right atrium, right ventricle, severe tricuspid regurgitation with a pressure gradient of 68 mm Hg, biventricular dysfunction, and a duct of 2 mm suggestive of severe pulmonary arterial hypertension. Neurosonography findings are normal. Abdominal ultrasonography findings are normal and there is no bleeding in the internal organs.

## PROGRESSION

The infant is started on respiratory support (mechanical ventilation), intravenous fluids, and inotropes. Emergent blood transfusion (20 mL/kg) is given in view of the severe anemia. Pulmonary hypertension improves over 72 hours, extubation is performed 47 hours after birth, and the infant receives oxygen for the next 2 days. The infant starts tube feeding on day 2, progresses to spoon feeds, and direct breastfeeding on day 5. Her hemoglobin concentration improves to 13.6 g/dL (136 g/L) after another blood transfusion of 10 mL/kg after an interval of 24 hours from the first transfusion. One investigation report at this stage reveals the diagnosis.

## DIAGNOSIS

Severe anemia at birth with no evidence of jaundice or splenomegaly is suggestive of blood loss. Absence of Rh or ABO settings and negative direct Coombs test result ruled out immune hemolysis. High reticulocyte count and the peripheral smear are suggestive of acute blood loss. In the absence of cord accidents and retroplacental clots, clear amniotic fluid, and normal neurosonography and abdominal ultrasonography findings, a diagnosis of fetomaternal hemorrhage (FMH) is considered. The diagnosis of FMH is confirmed with the Kleihauer Betke test on the mother, which shows abundance of fetal red blood cells (arrows show fetal erythrocytes in Fig) and fetal blood loss of about 180 mL.

## DISCUSSION

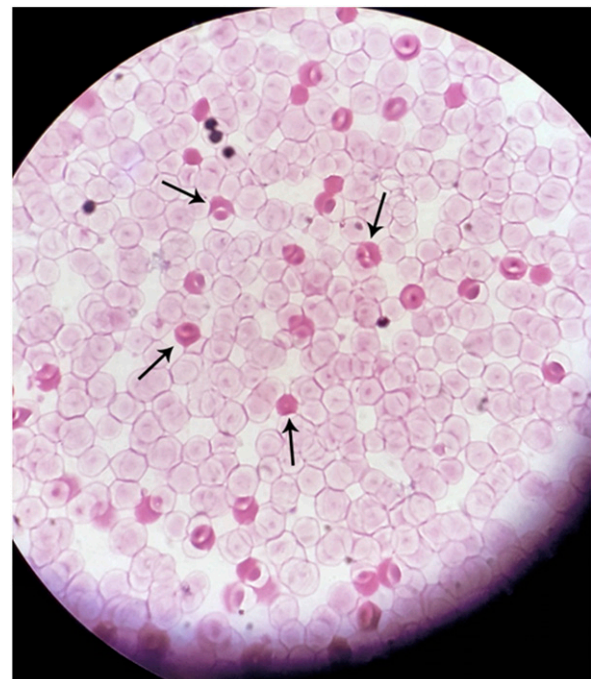
Fetal blood is likely to enter the maternal circulation in all pregnancies but without any clinical significance in most

cases. Expected fetal blood volume lost is small, with less than 0.025 mL of fetal red cells observed in 75% of cases, less than 0.5 mL in 96%, and less than 15 mL in more than 99%. (1)

The reported incidence of clinically significant FMH varies widely, depending on the volume of fetal blood considered meaningful. Considering the cutoff of 30 mL (amount of fetal blood covered by standard dose of Rh immunoglobulin), the incidence of FMH has been estimated to be approximately 3 per 1,000 live births. (2)

Although numerous risk factors have been described to correlate with the occurrence of FMH, more than 80% of cases with estimated blood loss greater than 30 mL remain unexplained. (2) Various conditions associated with FMH include blunt abdominal trauma, placental abruption, placental tumors, and also obstetric procedures such as amniocentesis, external cephalic version, and manual placental extraction.

The most common antenatal presentation of FMH is decreased or absent fetal movements, observed in nearly one-fourth of all cases. (3) Other less common findings are nonreassuring fetal heart tracings, sinusoidal pattern, fetal hydrops, and fetal growth restriction. (3) Most common postnatal presentation is unexplained anemia in the neonate.



**Figure.** Abundance of fetal red blood cells seen in the mother's blood specimen (arrows).

The diagnostic tests available for establishing the presence of FMH include the Rosette test, (4) Kleihauer Betke test, (5) and flow cytometry. (6) Of these, the Rosette test is a qualitative test and the other 2 are quantitative tests. The Kleihauer Betke test is currently most commonly used and the standard quantitative investigation for FMH. The test is based on the principle that hemoglobin F, a prominent component of fetal erythrocytes, is relatively resistant to acid elution compared with the hemoglobin of adult erythrocytes. So the maternal red blood cells appear clear as ghost cells and the fetal cells appear cherry red in color (arrows show fetal erythrocytes in Fig). These fetal cells are then counted under the microscope and reported as a percentage of adult cells. Although the Kleihauer Betke test is useful in identifying and quantifying FMH, it has its own limitations in the form of time taken for reporting and dependence on the skill of the technician for identifying fetal cells. It may underestimate or overestimate in case of poor staining of fetal cells, decreasing hemoglobin F in fetal cells and the presence of hemoglobin F in adult cells, respectively.

#### Lessons for the Clinician

- Fetomaternal hemorrhage should be suspected in all neonates presenting with severe anemia at birth.
- Kleihauer Betke test in the mother gives a quantitative estimation of fetomaternal hemorrhage.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the diagnosis and management of maternal/fetal blood loss such as placenta previa, placenta abruption, vasa previa, and maternal-fetal hemorrhage.

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### Case 1: A Neonate with Severe Pallor

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# Index of Suspicion in the Nursery

## 2 Recurrent Hypoglycemia in Early Neonatal Period

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### PRESENTATION

A female neonate is born at 40 weeks of gestation to a primigravida mother via caesarean section for a failed induction. History included second-degree consanguinity, with the mother having hypothyroidism (receiving thyroxine supplementation) and gestational diabetes mellitus (controlled on diet) antenatally. The neonate weighs 2.7 kg at birth, appropriate for gestational age. The postnatal transition is uneventful and she has no gross dysmorphic features. She continues to be exclusively breastfed and is hemodynamically stable throughout. On routine blood glucose monitoring (in view of the mother having gestational diabetes), she is found to have asymptomatic hypoglycemia with a blood glucose level of 36 mg/dL (2 mmol/L). On reexamination, she looks hyperpigmented compared to both her parents (Figs 1 and 2) without any virilization of genitals or hairy pinna. Neurologically she remains normal and abdominal examination does not reveal any hepatosplenomegaly. Her blood glucose remains less than 40 mg/dL (2.2 mmol/L) on multiple occasions in spite of supplemental formula feeds. Therefore she is admitted to the NICU, and is given glucose at a rate of 6 mg/kg per minute. Repeat blood glucose after 1 hour of starting intravenous 10% glucose is 58 mg/dL (3.2 mmol/L) and remains well within the normal range on continuous glucose infusion.

### DISCUSSION

#### Progression

Over the next 1 week, whenever an attempt is made to taper the glucose infusion rate, the infant develops recurrent episodes of hypoglycemia. Investigations are planned with the following differential diagnoses: sepsis, hyperinsulinism, defects of enzymes involved in glycogen storage, gluconeogenesis, fatty acid oxidation pathways, organic acidurias, and defects in hyperglycemic hormones such as glucagon, adrenalin, growth hormone, and cortisol. Normal hematologic indices (hemoglobin 15.3 g/dL [153 g/L], white blood cells 8,200/ $\mu$ L [ $8.2 \times 10^9$ /L], and peripheral blood smear normal) and C-reactive protein level excludes sepsis. Serum electrolytes and renal and hepatic function test results are all normal. Urine is negative for ketone bodies and reducing substances, and the insulin (5.2  $\mu$ U/mL) to glucose (74 mg/dL) ratio (0.07) is within normal range, thus excluding hyperinsulinism. No metabolic acidosis is seen, and normal lactate and ammonia levels rule out enzyme defects. Later tandem mass spectrometry of blood and gas chromatography mass spectrometry of urine are also reported to be normal,

**AUTHOR DISCLOSURE** Drs Sharma, Venkatnarayan, and Shaw have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





**Figure 1.** Striking hyperpigmentation in the infant as compared to her mother.

ruling out any inborn errors of metabolism. Investigations for endocrine insufficiency show morning cortisol levels to be less than  $0.5 \mu\text{g/dL}$  ( $13.8 \text{ nmol/L}$ ) and adrenocorticotrophic hormone (ACTH) levels to be greater than  $1,250 \text{ pg/mL}$  ( $275 \text{ pmol/L}$ ). So a primary diagnosis of glucocorticoid deficiency is made. The differential diagnosis includes congenital adrenal hyperplasia, which is ruled out because the 17-hydroxyprogesterone level is not raised, there are no signs of hyperandrogenism (no virilization), electrolyte levels are normal, and no evidence of adrenal hyperplasia is noted on ultrasonography and computed tomography (CT) scan of adrenal glands. CT of the adrenal glands also rules out any adrenal hemorrhage, trauma, and infection. Triple A syndrome (adrenal insufficiency, alacrimia, achalasia) is also excluded because the infant has normal esophageal patency.

#### Diagnosis/Management

Final diagnosis of familial glucocorticoid deficiency (FGD) is made in view of consanguinity, recurrent hypoglycemia, hyperpigmentation, markedly high ACTH levels, and low cortisol without evidence of increased sex steroids, or



**Figure 2.** Hyperpigmentation of entire skin.

mineralocorticoid deficiency and absence of adrenal hyperplasia. Homozygous stop gain mutation c.T60G (p.Y20X) of Exon 3 (NM\_206898) in the *MRAP* gene (Chr21: 33671342), a variant of unknown significance, was detected with Sanger sequencing (Fig 3).

Replacement treatment with hydrocortisone ( $10 \text{ mg/m}^2$  per day) was started as soon as the diagnosis of glucocorticoid deficiency was made (later changed to oral hydrocortisone  $1 \text{ mg/kg}$  per day), and there was no more hypoglycemic event. On follow-up until 1 year of age, the infant showed adequate weight gain, with normal neurologic findings.

#### The Condition

Neonatal hypoglycemia is commonly encountered in neonatal nurseries and NICUs, especially in low-birthweight neonates, including those with intrauterine growth restriction and those with diabetic mothers. (1) Recurrent hypoglycemia is rarer and should be looked for specifically in the presence of other clues noted in the neonate. The brain is almost entirely dependent on glucose for its metabolic needs and recurrent hypoglycemia can restrict brain growth. (2) Hence, it is extremely important to make a timely diagnosis and manage a case of recurrent hypoglycemia to prevent both short- and long-term morbidity and the associated mortality.



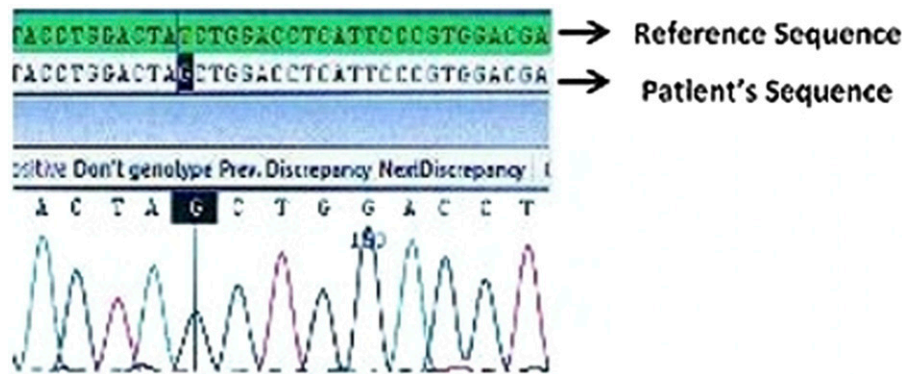


Figure 3. Sanger sequencing showing homozygous stop gain mutation *c.T60G* (*p.Y20X*) of Exon 3 (NM\_206898) in the *MRAP* gene.

FGD is a rare autosomal recessive disorder resulting from adrenal unresponsiveness to ACTH. This disease is characterized by low serum cortisol concentrations in the presence of grossly elevated plasma ACTH levels. Affected individuals typically present with recurrent hypoglycemia, hypoglycemic seizures, failure to thrive, recurrent infections, and hyperpigmentation. (3) The severe pigmentation of the skin is caused by the overstimulation of melanocortin 1 receptor (MC1R; cutaneous melanocyte-stimulating hormone [MSH] receptors) by high circulating MSH which is a byproduct of ACTH synthesis from proopiomelanocortin. This hyperpigmentation fades once proper treatment with glucocorticoids is initiated, which reduces ACTH concentrations. (4) Patients with FGD often present in late infancy or adolescence in view of nonspecific signs and symptoms and often after a stressful event. Positive family history of consanguinity, unexplained infant death, or having other affected family members supports the diagnosis. (5) The current patient was severely hyperpigmented at birth, which suggests that the fetal corticotrophs could produce excessive plasma ACTH in response to low fetal cortisol, which in turn, acted on melanocytes before birth.

#### Lessons for the Clinician

- Recurrent neonatal hypoglycemia is likely to be missed unless looked for specifically in the presence of risk factors.
- Familial glucocorticoid deficiency is an important cause of recurrent neonatal hypoglycemia, though it often

presents in late infancy or adolescence, usually after a stressful event.

- Increased pigmentation is an important clinical clue to the diagnosis of familial glucocorticoid deficiency.

### American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes.

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**Case 2: Recurrent Hypoglycemia in Early Neonatal Period**  
Saurabh Sharma, Kannan Venkatnarayan and Subhash Chandra Shaw  
*NeoReviews* 2019;20:e155  
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# Index of Suspicion in the Nursery

## 3 An Abnormal Nose Mass

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### PRESENTATION

A term, small-for-gestational age (3rd percentile) Southeast Asian female infant is born at 39 1/7 weeks via uncomplicated, spontaneous vaginal delivery to a 36-year-old gravida 5, para 5 mother. The pregnancy is complicated by gestational hypothyroidism, which is treated with levothyroxine. Prenatal ultrasonography showed normal fetal anatomy at 20 weeks. At birth, her Apgar scores are 9 and 10 at 1 and 5 minutes, respectively. Examination reveals a healthy-appearing, small-for-gestational age female infant in no cardiopulmonary distress with the following facial deformities: 1) a 1-cm subcutaneous deep blue cystic soft tissue mass just medial to the medial canthus of the left eye; 2) soft tissue swelling of the nasal bridge; 3) mild right-sided deviation of the superior aspect of the nose with an anterior bony void between the nasal bone and nasal cartilage on palpation; and 4) bilateral upslanting palpebral fissures and hypertelorism (Fig 1). A well-lubricated 5-Fr feeding tube is easily passed through the left nare. The initial diagnosis is a large dacrocystocele with potential nasal bone fracture from birth trauma. No imaging is undertaken because the infant is in stable condition. She is discharged from the hospital with her mother on day 2 after birth.

Around 2 weeks of age, she is evaluated by an otolaryngologist for an enlarging of the mass. Magnetic resonance imaging identified a left-sided frontal periorbital meningoencephalocele with complex solid and cystic elements and compression of the medial left rectus muscle with lateral deviation of the left globe (Fig 2).

### PROGRESSION

At 6 months of age, this infant underwent a single-staged surgical removal of the left-sided complex nasoethmoidal meningoencephalocele and facial reconstruction. She was followed by neurosurgery, craniofacial surgery, ophthalmology, and a complex care pediatrician alongside her primary pediatrician. Her surgical sites healed well. The pediatric ophthalmologist is closely following her for enophthalmos and suspected left-sided amblyopia secondary to the mass.

### DISCUSSION

Frontoethmoidal encephaloceles are a rare form of encephaloceles, and have the highest incidence in the Southeast Asian population, as in this case, with a frequency as high as 1 in 5,000 according to some authors. (1) The etiopathogenesis is uncertain, with theories including toxin, pesticide, or mold exposure as potential causes. (2) Associations with parental age, birth order, religious affiliation, gestational diabetes, or maternal folic acid levels do not appear to be inciting factors during fetal development. (3)

**AUTHOR DISCLOSURE** Dr Van Heukelom has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Left-sided nasal mass at birth.

Embryologically, the ectoderm fails to separate from the neuroectoderm around the 4th week of gestation and an open neural tube defect develops with a persistent sub-arachnoid connection. (4) After partial neural tube closure, neural crest cells form and migrate anterolaterally around the developing orbital structure to complete the anterior

encephalocele by about the 8th week of gestation. (5) If the lesion involves only the meninges, then an encephalocele is formed, compared with a meningoencephalocele, which has concurrent brain matter, as seen in this case. (2) Any exposure to potential triggers must have occurred before this stage of embryogenesis.

Anatomically, frontoethmoidal encephaloceles herniate anteriorly through the cribriform plate at various locations. (6) They are divided into nasofrontal encephaloceles, which appear at the root of the nose above the level of the nasal bones; nasoethmoidal encephaloceles (most common), which are situated inferior to the nasal bones; and naso-orbital encephaloceles (least common), which are typically not visible but can cause upper airway obstruction. (1) In general, anterior (facial) encephaloceles encompass frontoethmoidal (sincipital) and basal encephaloceles, which herniate through the sphenoid sinus. (6) Anterior encephaloceles compose about 20% of all head encephaloceles compared with posterior (scalp) encephaloceles, which make up around 80%. (2)

#### CLINICAL FINDINGS

Most congenital frontoethmoidal encephaloceles are typically identified during routine prenatal ultrasonography or on initial newborn assessment. They typically 1) present with an internal midline cranial defect corresponding to the site of failed neural tube closure, 2) are covered with at least an epithelial layer, and 3) will present as a soft, palpable

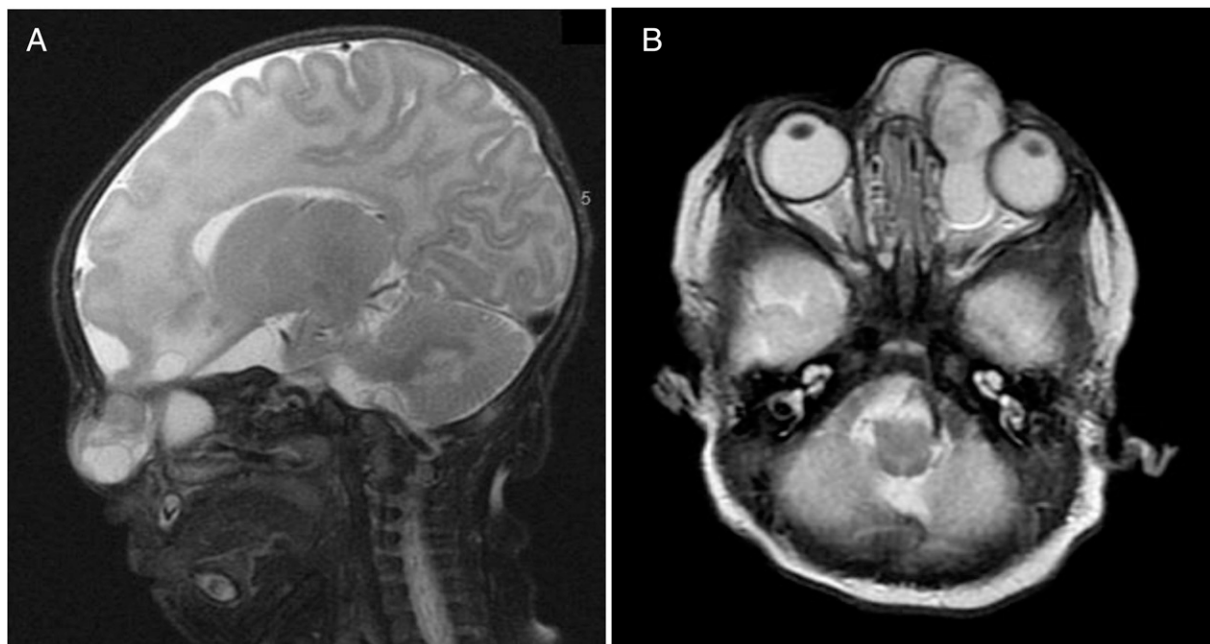


Figure 2. Magnetic resonance imaging scans. A. Sagittal view. B. Axial view.

mass. (1) They may transilluminate and can enlarge with an increase in cranial pressure such as crying or straining, or on application of the Valsalva maneuver. (2) The Furstenberg test, compression of the jugular veins, will also result in enlargement of the mass. (2) Ophthalmologic involvement includes hypertelorism, microphthalmia, strabismus, lacrimal duct obstruction, or decreased visual acuity. (7) Associated neural findings may include hydrocephalus (most common), microcephaly, anophthalmia, corpus callosum dysgenesis, or cortical atrophy. (4)

Maternal fetal  $\alpha$ -fetoprotein levels are rarely elevated because of the presence of overlying epithelium. (8) Magnetic resonance imaging is the preferred mode of diagnosis because of its superior ability to evaluate the presence of intracranial involvement. (4) Adjunct facial computed tomography scans identify osseous involvement. (4)

## DIFFERENTIAL DIAGNOSIS

Among nasal masses, encephaloceles are the most serious and need to be recognized early because of the potential risk for cerebrospinal fluid (CSF) leaks, meningitis, or intracranial abscess. (5) The differential diagnosis includes common nasal masses such as nasolacrimal duct mucocoeles, hemangiomas, lipomas, pilomatricomas, and rarer masses such as dermoid/epidermoid cysts and nasal cerebral heteropias (formerly gliomas). (4)

## TREATMENT

A single-staged combined craniofacial approach is the surgery of choice. (7) Meticulous planning with a multidisciplinary team is crucial. (6) Delayed surgical intervention until at least 6 months of age in stable children allows for growth of the facial structures and fewer anesthesia complications. (7)

Surgical goals are to provide a watertight closure of the dural defect at the skull along with craniofacial reconstruction and closure of any bony defects. (1) Untreated hydrocephalus may result in postoperative CSF leaks and must be corrected with a ventriculoperitoneal shunt before definitive surgery. (9) Intraoperative complications include blood loss, hypothermia, and electrolyte disturbances. (7)

## OUTCOMES

Outcomes are quite favorable for children with frontoethmoidal encephaloceles. With the absence of brain damage or herniation, normal intelligence and motor development can be achieved in most patients. (9) The poorest prognosis

involves patients with associated hydrocephalus or congenital brain anomalies such as microcephaly. (1) Nasal encephaloceles carry a low mortality, whereas surgery-related mortality is about 3%. (2) Deaths are typically secondary to postoperative complications such as meningitis or aspiration pneumonias. (2)

## Lessons for the Clinician

- Although rare, nasal encephaloceles need to be recognized early with appropriate evaluation and referral.
- There is a definite regional/ethnic predilection for those of Southeast Asian descent with uncertain etiopathogenesis.
- With isolated nasal encephaloceles and an appropriate multidisciplinary surgical team approach, outcomes are quite favorable.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the embryology, prevention, incidence, and differential diagnosis of myelomeningocele and encephalocele.
- Know the clinical and imaging findings, treatment, and outcome of myelomeningocele and encephalocele.

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### Case 3: An Abnormal Nose Mass

Jesse G. Van Heukelom

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## Intrauterine Growth Restriction with Abnormal Umbilical Artery Doppler Studies

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

**AUTHOR DISCLOSURE** Drs Hart and Young have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

#### Interpretation

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

- Bradycardia not accompanied by absent variability
- Tachycardia
- Minimal or marked baseline variability
- Absent variability without recurrent decelerations
- Absence of induced accelerations after fetal stimulation
- Recurrent variable decelerations with minimal or moderate variability
- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

- Absent variability with any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin* No.

106. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## CASE PRESENTATION

A 31-year-old gravida 1, para 0 woman at 31 3/7 weeks' gestation (based on last menstrual period consistent with first-trimester ultrasound scan) was admitted to the antepartum service for close inpatient fetal surveillance because of intrauterine growth restriction (IUGR) with absent end-diastolic flow demonstrated on umbilical artery Doppler assessment. She denied vaginal bleeding, contractions, and leakage of fluid, and reported active fetal movement at the time of admission.

This pregnancy was notable for a suspected velamentous placental cord insertion at the anatomic fetal survey. Given the association between a velamentous cord insertion and IUGR, the patient underwent serial fetal biometry for surveillance. The fetus was subsequently diagnosed with IUGR with an estimated fetal weight (EFW) less than the 10th percentile at 31 weeks' gestation. Umbilical artery Doppler assessment demonstrated absent end-diastolic flow. Her evaluation for IUGR included toxoplasmosis and cytomegalovirus serologic tests that demonstrated no evidence of prior exposure. Aneuploidy screening with noninvasive prenatal testing was low risk for chromosomes 13, 18, and 21.

She had no pertinent medical or surgical history. She had no toxic habits, recent illnesses, or medication exposures. She was normotensive at admission. The FHR tracing at admission is shown in Fig 1.

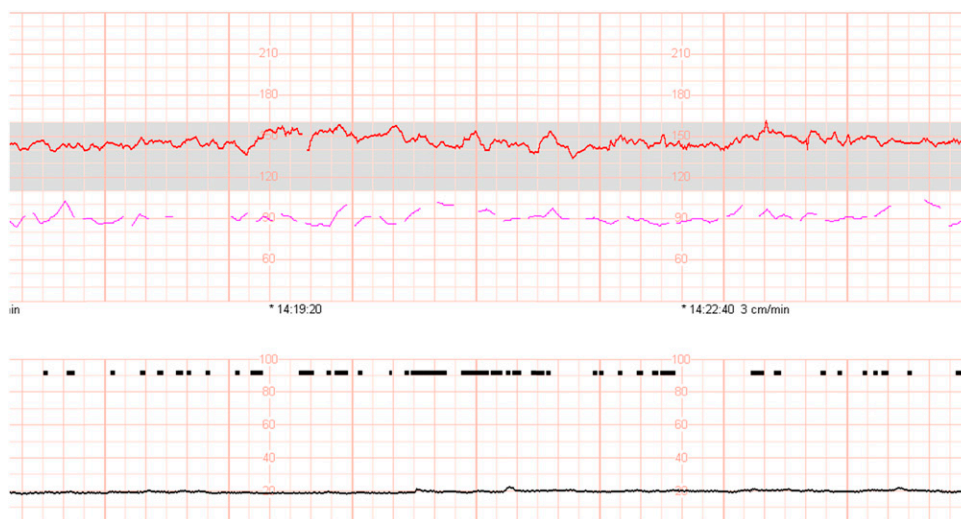


Figure 1. Electronic fetal monitoring strip 1.

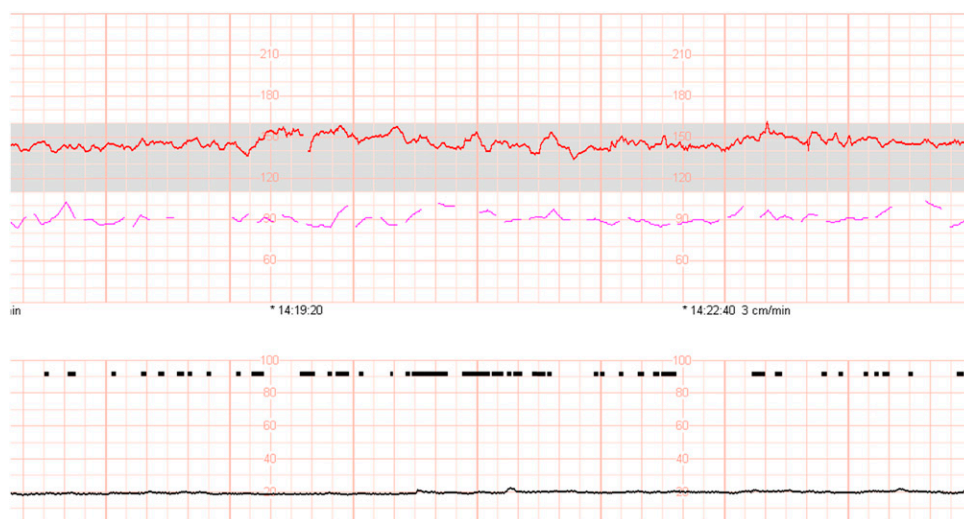


Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows (Fig 1):

- Variability: Moderate
- Baseline rate: 145 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category I
- Differential diagnosis: Reactive FHR tracing
- Action: No action necessary

## CASE PROGRESSION

Betamethasone was administered on the day of admission because of the increased likelihood of a preterm delivery. She underwent inpatient nonstress tests in the setting of the abnormal umbilical artery Doppler studies.

Repeat ultrasonography at 32 0/7 weeks' gestation demonstrated an EFW of 941 g (3rd percentile) with normal amniotic fluid volume. Interval fetal growth over the past 2 weeks was deemed appropriate. Umbilical artery Doppler measurements were elevated with persistent end-diastolic flow, with a systolic-diastolic ratio of 6.0. There was no absent or reversed end-diastolic flow on umbilical artery Doppler assessment at the time of this repeat ultrasonography. Given the reassuring fetal test result and the early gestational age, ongoing inpatient frequent fetal surveillance was recommended. Ongoing expectant management was recommended with a plan for delivery if fetal testing deteriorated or reversed end-diastolic flow of the umbilical artery Doppler developed. If absent end-diastolic flow on umbilical artery Doppler assessment was persistent, delivery at 34 weeks' gestation was recommended.

Later that day, the FHR tracing was nonreactive:

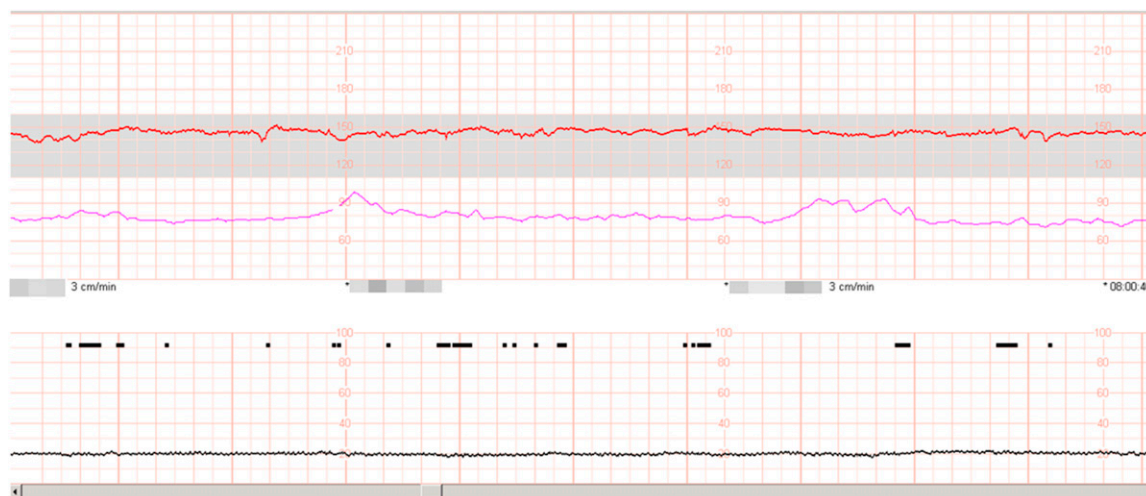


Figure 2. Electronic fetal monitoring strip 2.



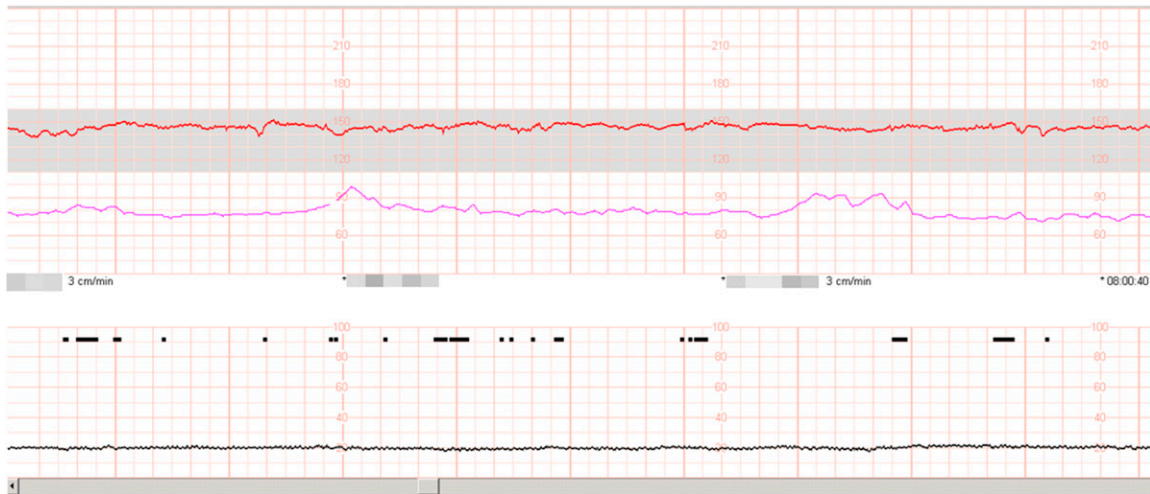


Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows (Fig 2):

- Variability: Moderate
- Baseline rate: 145 beats/min
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Nonreactive
- Differential diagnosis: Idiopathic, fetal sleep cycle, maternal drug ingestion, uteroplacental insufficiency

- Action: Ongoing external fetal monitoring, change maternal position, vibroacoustic stimulation, maternal ingestion of fluid, assess biophysical profile

A biophysical profile was reassuring; therefore, ongoing expectant management was recommended given the pre-term gestation.

At 32 1/7 weeks' gestation, the nonstress test was again nonreactive with a variable deceleration.

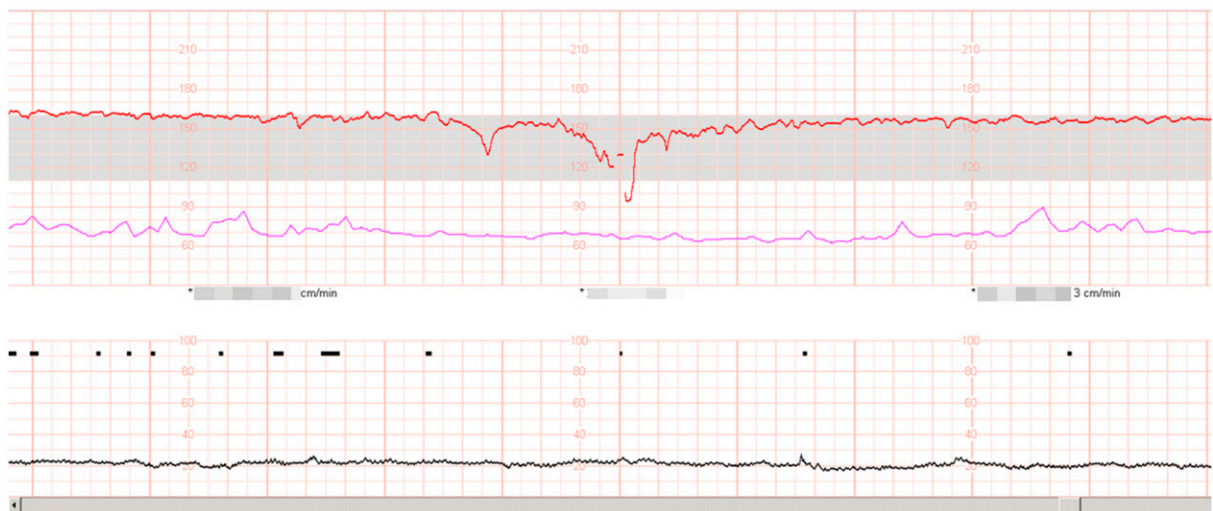


Figure 3. Electronic fetal monitoring strip 3.

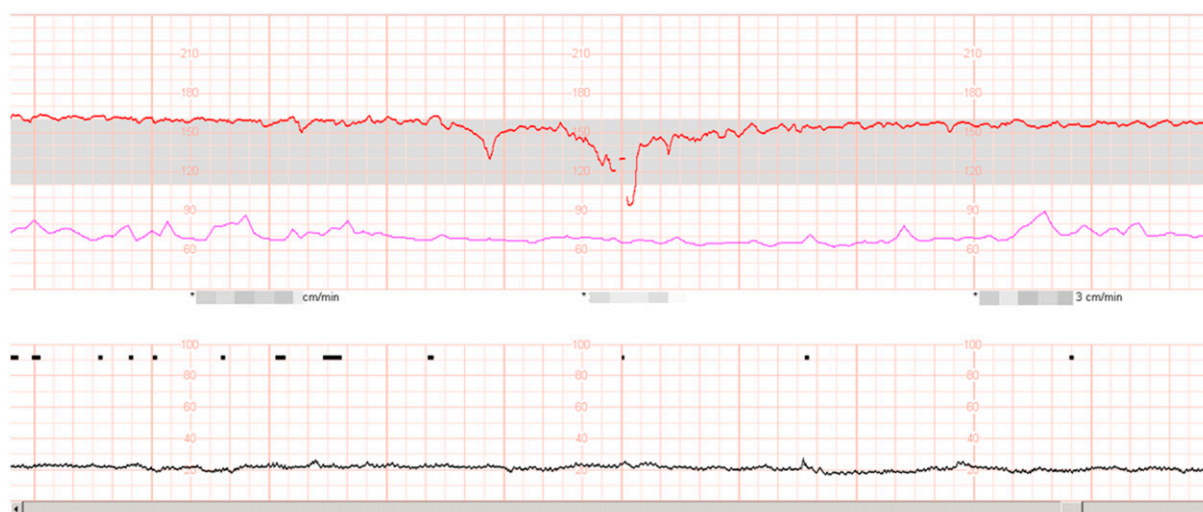


Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows (Fig 3):

- Variability: Moderate
- Baseline rate: 155 beats/min
- Episodic pattern: Variable deceleration lasting 30 seconds
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: FHR tracing with a variable deceleration
- Differential diagnosis: Cord compression, uteroplacental insufficiency, idiopathic
- Action: Continuous external fetal monitoring, change maternal position, obtain biophysical profile

The decision was made to transfer the patient to the labor and delivery department for continuous external fetal monitoring. Upon arrival at the labor and delivery department, the FHR tracing was notable for recurrent deep variable decelerations.

Findings from EFM strip 4 are as follows (Fig 4):

- Variability: Minimal and moderate
- Baseline rate: 165 beats/min
- Episodic pattern: Variable decelerations with nadir to 70 beats/min lasting 2 minutes in length
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: FHR tracing with recurrent spontaneous decelerations
- Differential diagnosis: Cord compression, uteroplacental insufficiency
- Action: Proceed with expedited delivery

The presence of recurrent decelerations raised the concern for placental insufficiency or fetal vessel compression within the velamentous cord. The spontaneous fetal

decelerations increased the likelihood of progression of these decelerations if induction of labor was attempted. Her obstetrical team recommended delivery via primary cesarean section because of recurrent spontaneous decelerations in the setting of IUGR and the abnormal fetal umbilical artery Doppler. The risk of an adverse fetal outcome with ongoing expectant management was thought to outweigh the risks of prematurity at a gestational age of 32 2/7 weeks' gestation; ongoing expectant management was not recommended given the concern for potential impending fetal compromise or stillbirth risk. The patient had completed her course of antenatal corticosteroids.

## OUTCOME

A viable male infant at 32 2/7 weeks' gestation was delivered via classic cesarean delivery weighing 1,020 g (2nd percentile) with Apgar scores of 7 at 1 minute and 8 at 5 minutes. Delayed cord clamping was performed. Clear amniotic fluid was present. The infant emerged active, with some inconsistent respiratory effort. He was brought to the warmer, wrapped in plastic, dried, and neonatal resuscitation assessment was initiated. He was stimulated and bulb suction was used. His initial heart rate was within normal limits without murmurs or pulse variation. His respiratory efforts improved. Supplemental oxygen was supplied based on Neonatal Resuscitation Program guidelines, and the infant was placed on continuous positive airway pressure (CPAP). He was shown to the parents and then transferred to the NICU.

In the NICU, the infant made a transition from CPAP to room air 1 day after birth. He had no significant complications during his hospital course. He was discharged from the hospital at a weight of 2,075 g after a 41-day stay in the NICU.

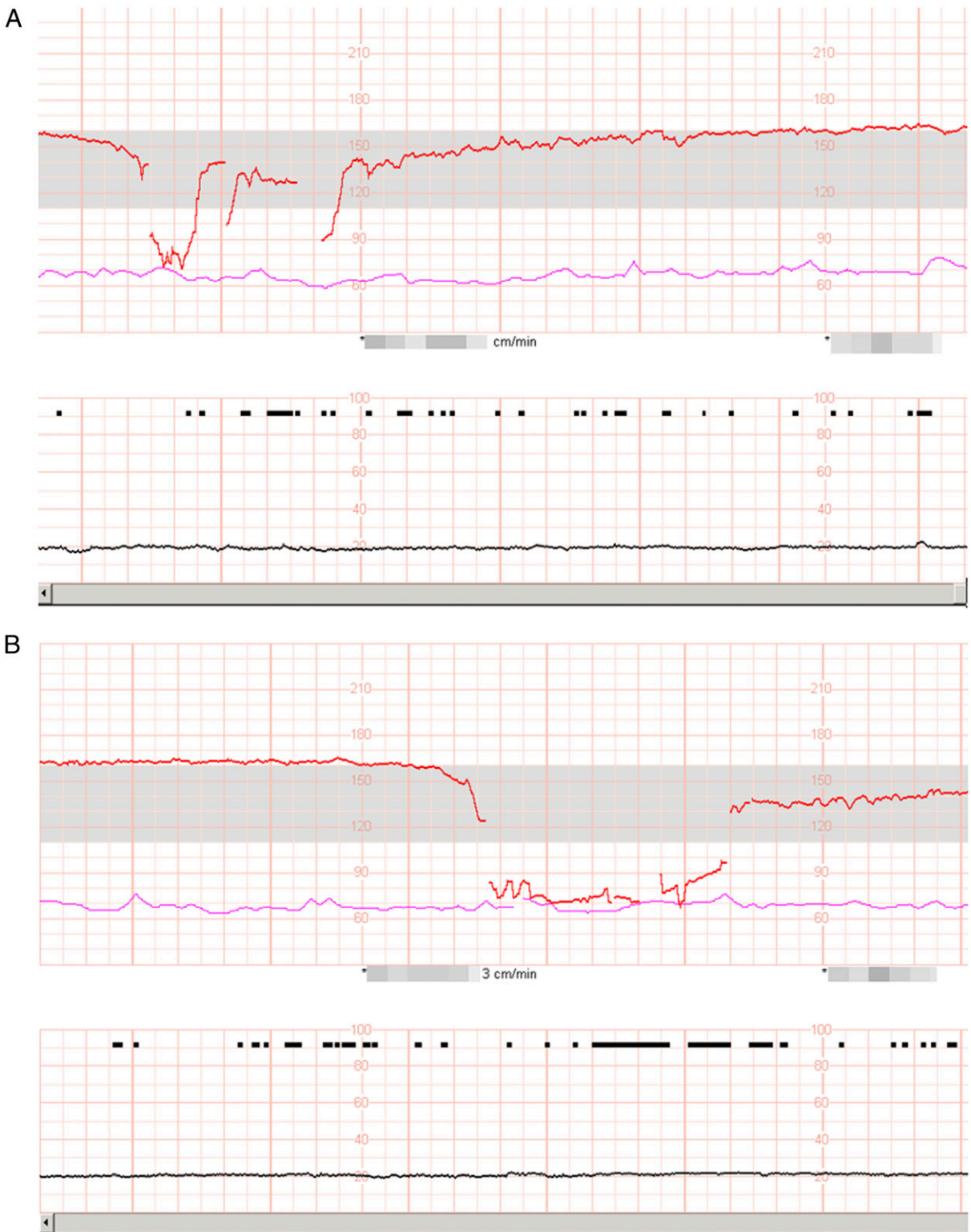


Figure 4. Electronic fetal monitoring strip 4.

Placental pathology demonstrated a singleton placenta weighing 141 g (<10th percentile for gestational age) with an unremarkable, 3-vessel umbilical cord

that inserted marginally into the placental disc. The small placental disc was noted to have accelerated villous maturation, distal villous hypoplasia, and infarcts (<5%

of disc volume) consistent with maternal vascular malperfusion.

## DISCUSSION

IUGR is defined by obstetricians as an ultrasonographic EFW less than the 10th percentile for gestational age. (1)(2) This definition, however, does vary in the obstetric literature, and at times EFW cutoffs of less than the 3rd or 5th percentiles have also been used to define fetal growth restriction. (3) Multiple groups have tried to clarify and standardize this definition to optimize outcomes and differentiate the physiologically normal fetus that is constitutionally small from the pathologically growth-restricted fetus. (4) The definition of IUGR does not take into account fetal growth potential, and thus, pathologic growth restriction may be misdiagnosed. (2) Some providers advocate for individualized fetal growth assessment by ethnicity or genetic growth potential to create a more individualized model. However, use of a customized growth curve is not standard. (3) A newborn who is small for gestational age (SGA) has a birthweight that is less than the 10th percentile for gestational age. (2)

The most common cause of IUGR in an SGA neonate is constitutional smallness. As indicated earlier, differentiating between constitutional small size and pathological growth restriction can be challenging. The etiologic factors for IUGR can be separated into maternal, fetal, and placental categories. Maternal preexisting medical conditions can increase the risk for placental insufficiency and IUGR, including but not limited to, hypertensive disorders, antiphospholipid antibody syndrome, autoimmune diseases, diabetes, renal disease, and cardiac disease. In addition, many teratogen exposures and toxic substances such as tobacco, cocaine, and/or alcohol have been associated with IUGR. Potential fetal etiologies include genetic and structural disorders. Often, fetal chromosomal abnormalities or anatomic anomalies such as gastroschisis or congenital heart disease can be associated with IUGR. Congenital fetal infections such as cytomegalovirus, toxoplasmosis, and rubella may result in IUGR. Both placental and umbilical cord abnormalities, such as placental infarction, velamentous cord insertion, or marginal cord insertion, may increase the likelihood of fetal growth restriction. (3) A placental cord insertion within 2 cm of the edge of the placenta is defined as a marginal cord insertion, in contrast to a velamentous cord insertion, which occurs when vessels insert into membranes distant from the placental edge.

IUGR increases the risks of intrauterine death, as well as neonatal morbidity and mortality. Furthermore, there is concern that fetal growth restriction predisposes children

to the development of potential cognitive delays, as well as obesity, type 2 diabetes, coronary artery disease, and stroke as adults. (1)(2) IUGR newborns are predisposed to short-term issues such as hypoglycemia and hypothermia. Other risks for a growth-restricted neonate include perinatal complications, neurologic abnormalities, and increased mortality. (2)

If IUGR is suspected, further evaluation with umbilical artery Doppler should be considered. A full survey of fetal anatomy should be obtained if not previously performed, and an evaluation for possible etiologies of the IUGR including infections or genetic abnormalities can be considered. (1) Umbilical artery Doppler velocimetry assesses the resistance of blood perfusion to the fetoplacental unit. (1) Abnormal umbilical artery Doppler measurements showing absent or reversed end-diastolic flow are associated with increased perinatal mortality. (2) Additional potential markers of adverse neonatal outcomes include oligohydramnios and an EFW less than the 3rd percentile. (2)(4) Most fetuses with suspected IUGR can be delivered at term. The decision for a preterm delivery is based on abnormal Doppler findings and fetal testing results.

Optimal timing for delivery of fetuses with suspected IUGR may vary based on the underlying etiology of the fetal growth restriction. (2) The Society for Maternal Fetal Medicine, American College of Obstetrics and Gynecology, and the Eunice Kennedy Shriver National Institute jointly suggest the following strategies for late preterm and early term delivery in the setting of a singleton gestation with IUGR and otherwise reassuring fetal testing:

- Delivery between 38 0/7 and 39 6/7 weeks of gestation if isolated IUGR
- Delivery between 34 0/7 and 37 6/7 weeks of gestation with additional risk factors including oligohydramnios, maternal risk factors/comorbidities, or abnormal umbilical artery Doppler velocimetry.
- Delivery at 32 0/7 weeks of gestation if reversed end-diastolic flow is noted (2)(3)

In this case, the etiology of the fetal growth restriction was thought to be secondary to placental insufficiency and an abnormal cord insertion. With close fetal surveillance, a reassuring neonatal outcome was achieved.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Describe the significance of abnormal umbilical artery Doppler studies in the setting of intrauterine growth restriction.

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## Strip of the Month: Intrauterine Growth Restriction with Abnormal Umbilical Artery Doppler Studies

Jessica M. Hart and Brett C. Young

*NeoReviews* 2019;20:e161

DOI: 10.1542/neo.20-3-e161

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## Microcephalic Newborn with Forehead Nevus Flammeus, Bulging Eyes, and Clenched Fists

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### THE CASE

A 35-day-old growth-restricted black female infant presents with a triangular head, glabellar nevus flammeus, exophthalmos, flexion contractures of hands, micro-retrognathia, and stridor (Fig, A and B).

### Prenatal and Birth Histories

- Mother is an 18-year-old gravida 1 para 0 black woman
- Pregnancy was complicated by intrauterine growth restriction (IUGR) of unclear etiology and nonobstructive polyhydramnios with a normal fetal anatomical survey
- Induced vaginal delivery for IUGR
- Estimated gestational age at birth: 37 weeks
- Prenatal laboratory findings: Group B *Streptococcus* negative; hepatitis B surface antigen negative; rapid plasma reagin nonreactive; HIV negative; rubella immune; *Chlamydia* infection during pregnancy treated adequately
- Apgar scores: 2 and 8 at 1 and 5 minutes, respectively; infant initially had no respiratory effort but responded to stimulation and did not require positive-pressure ventilation
- Symmetric small-for-gestational age: Birthweight 1,500 g, length 41 cm, head circumference 32.5 cm (all <3rd percentile)

### Presentation

The infant was transferred to the NICU from an outside hospital at 1 month of age because of poor feeding, stridor, and multiple dysmorphic facial features.

### CASE PROGRESSION

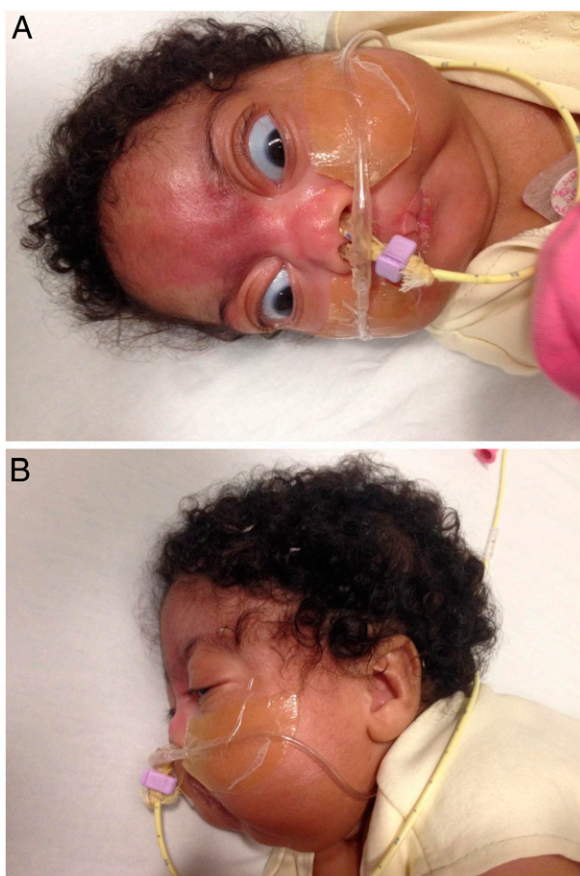
#### Vital Signs–Day 35

- Heart rate: 150 beats/min
- Respiratory rate: 42 breaths/min
- Temperature: 98.8°F (37.1°C)
- Oxygen saturation: 95% on 4 L/min high-flow nasal cannula

#### Physical Examination–Day 35

- Growth parameters
  - Weight: 2.09 kg (<3rd percentile for age)
  - Length: 41 cm (<3rd percentile for age)

**AUTHOR DISCLOSURE** Drs Sharma, Hu, Geddes, and Acharya have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



**Figure.** A. Glabella nevus flammeus, exophthalmos, hypertelorism and triangular shaped head. B. Microretrognathia and anteverted nares.

- Head circumference: 32.5 cm (<3rd percentile for age)
- Head
  - Microcephaly with a triangular shaped head
  - Bilateral exophthalmos and hypertelorism
  - Anteverted nares, high arched intact palate
  - Micrognathia, retrognathia
- Lungs
  - Coarse breath sounds with upper airway congestion and inspiratory stridor
  - Tachypnea and mild subcostal retractions
- Cardiovascular: Normal S1 and S2, regular rate and rhythm, grade 2/6 murmur, 3+ pulses, capillary refill <3 seconds
- Abdomen: Soft, nondistended, no hepatosplenomegaly, normal bowel sounds
- Genitourinary: Normal female genitalia
- Skeletal: Back and spine normal, no hip clicks
- Neurologic: Hypertonic upper extremities, truncal hypotonia
- Extremities: Overlapping fingers bilaterally, clenched fists
- Skin: Pink, intact, nevus flammeus on center of forehead

### Laboratory Studies

- Complete blood cell count: White blood cells:  $11.7 \times 10^3/\mu\text{L}$  ( $11.7 \times 10^9/\text{L}$ ), with 48% neutrophils, 32% lymphocytes, 13% monocytes
- Hemoglobin: 10.2 g/dL (10.2 g/L)
- Platelets:  $407 \times 10^3/\mu\text{L}$  ( $407 \times 10^9/\text{L}$ )
- Capillary blood gas: pH 7.32,  $\text{PCO}_2$  62 mm Hg (8.2 kPa),  $\text{PO}_2$  55 mm Hg (7.3 kPa), bicarbonate 31 mEq/L (31 mmol/L), base excess +4 mEq/L
- Electrolyte panel: Normal
- Blood culture: No growth
- Newborn screen: Normal
- Chromosomal analysis and microarray: Normal

### Imaging Studies

- Chest radiography: Normal cardiothymic silhouette with no focal consolidation, pleural effusion, pneumothorax, or air space disease
- Radiography of the hands: Normal bone maturation
- Head ultrasonography: Normal
- Renal ultrasonography: Normal
- Echocardiography: Moderate-sized patent ductus arteriosus with left-to-right shunting
- Brain magnetic resonance imaging: Dysgenesis of the corpus callosum and bilateral orbital proptosis

### Other Studies

- Ophthalmologic examination: Bupthalmos, no colobomas, and normal optic nerves
- Hearing screen: Failed bilaterally

The infant's respiratory distress worsened during her hospital stay, with a need for continuous noninvasive positive pressure ventilation. Flexible laryngoscopy with rigid bronchoscopy showed severe laryngomalacia, mild tracheomalacia, and base of tongue obstruction. A sleep study confirmed severe obstructive sleep apnea. Because of the severe laryngomalacia and inability to wean from positive pressure ventilation, a primary supraglottoplasty was performed. Following this, the infant could be weaned to nasal cannula. However, she showed no improvement in oral feeding skills, and had significant reflux and failure to thrive, requiring nasogastric tube feedings.

### DIFFERENTIAL DIAGNOSIS

Glabellar nevus flammeus, exophthalmos-hypertelorism, high arched palate, microretrognathia in an infant with IUGR with laryngomalacia, poor weight gain, and severe feeding difficulties.

- Bainbridge-Ropers syndrome (*ASXL3* syndrome)
- Bohring-Opitz syndrome
- Cornelia de Lange syndrome
- Marshall-Smith syndrome
- Shashi-Pena syndrome (*ASXL2* syndrome)

## ACTUAL DIAGNOSIS

### Bohring-Opitz Syndrome (BOS)

Based on the infant's clinical, laboratory, and radiographic findings, our primary diagnostic considerations were BOS and Marshall-Smith syndrome. Genetic testing for Marshall-Smith syndrome with nuclear factor IX (*NFIX*) sequencing returned with no variants. Testing for BOS with additional sex combs-like 1 (*ASXL1*) sequencing demonstrated a pathogenic variant confirming this diagnosis.

Following confirmation of the BOS diagnosis, comfort care was suggested as an option, in view of the poor outcomes associated with this syndrome. However, the family did not wish to pursue this option and the infant continued to receive maximal interventions. The infant was discharged from the hospital with oxygen and nasojunal feedings with close follow-up. She was readmitted to the hospital multiple times after discharge for various reasons. At 6 months of age, the infant was brought to the emergency department in pulseless arrest following a seizure at home and died, despite extensive cardiopulmonary resuscitation.

## WHAT THE EXPERTS SAY

BOS is a rare malformation syndrome characterized by distinctive facial features, severe IUGR with postnatal growth failure, profound intellectual disability, and feeding difficulties. (1) It should be suspected in individuals with the following clinical features (note: features marked with an asterisk (\*) are observed in 100% of cases confirmed with molecular testing). (2)(3)

1. Craniofacial appearance
  - Microcephaly\* or trigonocephaly/prominent metopic ridge
  - Glabellar and eyelid nevus flammeus (simplex) that fades with age
  - Prominent globes\*
  - Cleft lip
  - Palatal anomalies: Cleft palate, high arched palate, or prominent palatine ridges
  - Micrognathia and/or retrognathia
2. Growth and feeding
  - IUGR
  - Severe feeding difficulties\* with chronic emesis
  - Poor postnatal weight gain and linear growth

3. Neurologic
  - Global developmental delay or intellectual disability (severe-to-profound range)\*
  - Seizures\*
4. Respiratory
  - Recurrent infections (commonly respiratory) in early childhood that improve with age
5. Sleep
  - Sleep disturbance
  - Obstructive sleep apnea
6. Ophthalmologic
  - High myopia presenting in infancy that may worsen over the first years of age
  - Variable optic nerve and retinal anomalies
7. BOS posture\*
  - Flexion at the elbows with ulnar deviation and flexion of the wrists and metacarpophalangeal joints
  - Truncal hypotonia with hypertonia of the extremities

The diagnosis of BOS is established in a proband with suggestive clinical features and/or by identification of a germline heterozygous pathogenic variant in the *ASXL1* gene on molecular genetic testing. The *ASXL1* gene, located on 20q11.21, is involved in the activation and silencing of the *HOX* genes, which are involved in forming body structures and chromatin remodeling. (4) The prevalence is unknown; of 46 clinically diagnosed individuals reported in the literature, the diagnosis was confirmed with molecular testing in only 20. (3)

The mortality rate remains high (40%), mostly in early childhood because of unexplained bradycardia, obstructive apnea, and pulmonary infections, with approximately 25% of deaths occurring before age 1 year. If the patient survives early childhood, feeding difficulties and recurrent infections become less concerning. Failure to thrive and severe-to-profound developmental delay are universal. (5)

In the current patient, the classic phenotype of distinctive facial features in the setting of IUGR and poor feeding led us to sequence the *ASXL1* gene for BOS. BOS is closely related to 2 other syndromes associated with mutations in the *ASXL* gene, as listed in the differential diagnoses.

In Shashi-Pena syndrome, caused by a mutation in the *ASXL2* gene and closely related to BOS, features such as glabellar nevus flammeus, prominent eyes, and feeding difficulties are present, but these infants typically are macrocephalic and usually do not have growth restriction. In general, their prognosis tends to be more variable and usually less severe than in BOS. (6) In Bainbridge-Ropers syndrome, caused by a mutation in the *ASXL3* gene, growth restriction, prominent glabella, anteverted nares, and severe psychomotor restriction are features shared with BOS, but

trigonocephaly, glabellar nevus flammeus, and the characteristic “BOS posture” are absent. (7)

The other 2 considerations in the differential diagnoses were Marshall-Smith syndrome and Cornelia-de-Lange syndrome. Marshall-Smith syndrome is characterized by upper airway obstruction, proptosis, and corpus callosum hypoplasia, as seen in this infant; however, this infant did not have accelerated skeletal maturation and did not have any variants in *NFIX*. (8) Similarly, infants with Cornelia-de-Lange syndrome often have eye abnormalities, microcephaly, and distinctive facial features, but do not have the characteristic glabellar nevus flammeus rash that was seen in this infant, nor do they typically have respiratory problems. (9)

In summary, BOS is a clinically recognizable syndrome. Careful attention by the treating clinician/neonatologist to the classic facial features can direct specific genetic testing and lead to early diagnosis and effective counseling.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical features and know how to diagnose and manage craniofacial anomalies.

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# Microcephalic Newborn with Forehead Nevus Flammeus, Bulging Eyes, and Clenched Fists

Megha Sharma, Xiangxin Hu, Gabrielle C. Geddes and Krishna Acharya

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## Delayed Umbilical Cord Clamping in Preterm Infants

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Video 1. Delayed Cord Clamping in a Cesarean Delivery. Click here to view the video.



Video 2. Delayed Cord Clamping in a Vaginal Delivery. Click here to view the video.

Please view these 2 videos showing delayed cord clamping of a preterm infant born via cesarean delivery and a preterm infant born via vaginal delivery.

Which of the following scenarios is an absolute contraindication to delayed cord clamping?

- A. Infant born due to severe maternal HELLP syndrome
- B. Infant with placental separation immediately after delivery
- C. Infant with trisomy 21
- D. Premature infant at 23 weeks' gestation
- E. Twin gestation

**AUTHOR DISCLOSURE** Drs Josephsen, Buchanan, and Strand have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

There is a growing body of evidence that delaying umbilical cord clamping in preterm infants may improve neonatal outcomes by increasing infant blood volume through placental transfusion. (1) Better outcomes may include improved neonatal transition, decreased intraventricular hemorrhage, decreased necrotizing enterocolitis, and decreased mortality. (1)(2)(3) Term infants receiving delayed cord clamping have evidence of increased hemoglobin levels in the immediate newborn period, as well as a reduction in iron deficiency at 3 to 6 months of age. (4) Most published studies define cord clamping as "delayed" when at least 30 to 60 seconds elapse before clamping the cord after birth. However, the optimal timing for clamping of the umbilical cord is unknown. An early study of term infants suggested that the transfused blood volume increases 2-fold between 30 and 60 seconds of delay (from 10 mL/kg to 25 mL/kg), (5) but human studies of volume differences by time in premature infants are lacking. The delayed cord clamping procedure appears to be safe for both the mother and newborn, but its implementation may be challenging, because it represents a substantial change in practice compared with immediate cord clamping in preterm infants. (6)

Because of the potential benefits of delayed cord clamping, the American Academy of Pediatrics has endorsed the 2017 American College of Obstetricians and Gynecologists committee opinion on delayed cord umbilical cord clamping after birth, which concludes that "delayed umbilical cord clamping for at least 30 to 60 seconds is recommended in term and preterm infants except when immediate umbilical cord clamping is necessary because of neonatal or maternal indications." (7)(8) In addition, the current 7th edition of the Neonatal Resuscitation Program remarks that "evidence suggests that cord clamping should be delayed for at least 30 to 60 seconds" for most infants. (9)

Contraindications to delayed cord clamping are few and include the following:

- maternal hemorrhage
- need for immediate neonatal resuscitation
- disrupted placental circulation such as placental abruption, previa, or cord avulsion (7)

There are no current guidelines for an infant with a congenital anomaly that does not require immediate resuscitation such as gastroschisis or congenital heart disease; delayed cord clamping may still be considered. Twin gestation is not a contraindication and has been successfully described. (10) The obstetrical and neonatal teams should communicate directly if concerns about the pregnant woman or infant are present.

The safety of delayed cord clamping has been evaluated for mothers and infants. In a recent meta-analysis, maternal safety parameters of postpartum hemorrhage, maternal blood transfusion rates, or the need for manual removal of the placenta were not different when compared with immediate cord clamping. (11) In preterm infants, multiple studies have failed to show an increase in jaundice requiring phototherapy, polycythemia, or a difference in infant admission temperature. (1)(12) However, an increase in jaundice requiring phototherapy has been noted in term infants receiving at least 30 seconds of delayed cord clamping. (4) Maternal and infant safety has also been demonstrated in twins. (10)

Placement of the infant during the delayed cord clamping procedure depends on the mode of delivery. For vaginal deliveries, holding the infant at the introitus is feasible, but the use of a small table or commercially available trolley has also been described. (13)(14) For cesarean deliveries, the premature infant can be supported on the maternal legs below the incision. Alternatively, if the umbilical cord length is sufficient, the infant could be placed on a small table or trolley just beside the mother. The effect of gravity appears to have only minor effects on placental transfusion volume, suggesting that any of these placement positions are acceptable. (15)(16)(17)

This training video demonstrates the delayed cord clamping procedure for cesarean and vaginal deliveries of preterm infants. Thermoregulation is prioritized by wrapping the infant in a sterile plastic drape to maintain body temperature. Infant temperature is also maintained by the warm placental blood transfused through the umbilical cord. The neonate is held just below the level of the introitus for vaginal deliveries and placed on the maternal legs just below the incision for cesarean deliveries. A designated time keeper calls time at prespecified intervals, based on hospital preference (15 seconds in these videos). Infant breathing should be encouraged with gentle stimulation, because lung inflation during delayed cord clamping improves cardiovascular function in preterm lamb models. (16) Of note, this technique was not represented well in the videos (ie, during the procedure, the obstetrical clinicians should have been rubbing the infant's back to encourage respiratory effort). This video provides an excellent example of ideal communication between the obstetrical and neonatal teams from the predelivery briefing until the umbilical cord is ultimately cut, which is the key to success of this intervention.

Correct answer is B. Infant with placental separation immediately after delivery.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the rationale, risks, and benefits of delayed cord clamping.

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**When to Include a Lumbar Puncture in the Evaluation for Neonatal Sepsis:** 1. D; 2. A; 3. B; 4. B; 5. E.

**Antibiotic Resistance in the Neonatal Intensive Care Unit:** 1. D; 2. C; 3. E; 4. C; 5. B.

**Delayed Umbilical Cord Clamping in Preterm Infants**  
Justin B. Josephsen, Christopher Q. Buchanan and Marya L. Strand  
*NeoReviews* 2019;20:e174  
DOI: 10.1542/neo.20-3-e174

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## Implementation of the Korean Neonatal Network

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### Abstract

Although there has been a marked increase in the number of NICUs in Korea, the gap in quality improvement has remained a national focus. The Korean Neonatal Network (KNN) was established in 2013 by the Korean Society of Neonatology with support from the Korea Centers for Disease Control and Prevention, with the aim of improving neonatal outcomes by offering data-driven interactive tools to all participating NICUs. Approximately 2,000 very-low-birthweight (VLBW) infants from 70 participating hospital NICUs are registered annually in the KNN, with a total of over 12,000 to date. In addition to providing a national registry of VLBW infants, this unique system also leads to an infrastructure for quality improvement in neonatal care, which in turn has an effect on the development of evidence-based neonatal medicine in Korea. Furthermore, it is encouraging that the KNN plans to develop tools to facilitate multicenter clinical trials and to join the global international network for international collaboration.

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### ABBREVIATIONS

BPD	bronchopulmonary dysplasia
e-CRF	electronic case report form
GA	gestational age
IVH	intraventricular hemorrhage
KCDC	Korea Centers for Disease Control and Prevention
KNN	Korean Neonatal Network
NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
OR	odds ratio
PDA	patent ductus arteriosus
PVL	periventricular leukomalacia
QI	quality improvement
ROP	retinopathy of prematurity
VLBW	very-low-birthweight
VON	Vermont Oxford Network

### INTRODUCTION

The Korean Neonatal Network (KNN) was established on April 15, 2013, by the Korean Society of Neonatology, with support from the Korea Centers for Disease Control and Prevention (KCDC). (1) The KNN aimed to plan appropriate health-care policies for high-risk newborns by establishing a nationwide web-based registry for very-low-birthweight (VLBW) infants by providing population-based national key data. The KNN provides data-driven interactive tools for quality improvement (QI) to participating NICUs to help improve neonatal outcomes. Furthermore, the KNN aims to establish effective evidence-based strategies to increase the survival rate and to reduce complications in high-risk newborns, thereby reducing the socioeconomic burden by decreasing medical costs. This will ultimately result in improvements in the health of newborns in Korea, a country with an extremely low birth rate.

The KNN has obtained the cooperation and allegiance of neonatologists, neonatal nurses, and other specialists who volunteer their time and effort to participate in the network. It contributes to new knowledge about newborn

medicine and provides the foundation for centers that want to assess their performance through comparison of clinical data within the network. Various networks have been established for benchmarking, and consequently, implementing QI efforts such as national population-based networks, regional networks, academic networks with selected membership, networks with open membership, and corporate health-care provider networks. (2)(3) The KNN will not only be a national registry for VLBW infants but will also provide an infrastructure that aids multicenter clinical trials as well as QI efforts in neonatal care, thus contributing to the development of evidence-based neonatal care in Korea. In this review, we describe the implementation of the KNN and its activities.

## THE MEDICAL ENVIRONMENT IN KOREA

South Korea, a peninsula bordering China and Russia in East Asia, has a population of a little over 51 million people living in 99,720 square miles. In Korea, there is a nationwide comprehensive compulsory health-care program, the National Health Insurance, which serves the entire population, and a medical aid program for low-income households (about 3% of the population). This program is operated by the National Health Insurance Corporation and regulated by the Ministry of Health, Welfare, and Family Affairs of the Korean Government. At the end of 2013, 97.3% of the population was covered by this service. (4)

## DEMOGRAPHIC STATISTICS

The total Korean population in 2017 was 51.42 million, of which 49.9% were female. Total annual number of births was 357,771, with a fertility rate of 1.05 children per woman. Crude birth rate was 7.0 (per 1,000 people). In 2017, the number of preterm births was 27,120 (7.6%). The average age of pregnant women most commonly was between 30 and 39 years, with 71% of births occurring to women in this age range in 2017; in contrast, in 2000, the most common maternal age for births was between 20 and 29 years, with 63% of births to women in this age range. (5) Various social changes, including increased maternal age and the subsequent greater infertility rate with more support from assisted reproductive technologies, have resulted in a remarkable rise in the number of multiple pregnancies and preterm births, leading to an absolute increase in high-risk infant births. (6)

## VIABILITY

The limits of viability for premature infants have consistently decreased in parallel to advancements in overall medical care. According to the Neonatal Resuscitation Guidelines from the American Heart Association, a neonatal resuscitation team can provide comfort care rather than aggressive resuscitation to infants born at less than 22 weeks' gestational age (GA). (7) Decisions differ depending on the actual situation in each country and center. In Korea, a GA between 22+0/7 and 23+6/7 weeks is generally considered to be the low end of the viability range when infants can become candidates for selective resuscitation. However, a preterm infant born at 21+5/7 weeks of gestation, the youngest survivor to date, continues to survive without severe neurodevelopmental impairment at 43 months of age, at the time of this writing. (8) Also, between 2013 and 2014, infants who were born at 22 and 23 weeks of gestation and received active resuscitation were reported to have survival rates of 13.8% and 41.1%, respectively. (9)

## LEVEL OF NICU CARE

To deliver efficient perinatal and neonatal intensive care, the governments of most developed countries have created a strong network system, with appropriate levels of NICU care and nationwide regionalization. In the United States, the perinatal and neonatal management was classified into 3 levels in 1975 and a regionalized care system and centralized transfer service were implemented. (10)(11) In the 1980s, Japan successfully initiated the building of perinatal care and transport systems by starting the regionalization of perinatal care centers and expanding their scope to establish perinatal emergency care systems in each prefecture across the country. (12)

In Korea, the government recognized the necessity for quantitative expansion of NICUs nationwide because of an estimated shortage of 500 to 600 NICU beds as well as severe regional disparity. (13) The regional NICU Support Project (outside Seoul) was initiated by the Ministry of Health and Welfare in 2008. (13) By 2016, a total of 430 NICU beds were provided to 56 regional hospitals, with a total investment of \$50 million and approximately \$70,000 equivalent of annual funding per bed to enhance the infrastructure of Korean NICUs. (14) In addition, the government increased the daily reimbursement of NICU admission charges almost 2-fold to compensate for high medical costs, nursing care fees, and various medical charges; over time, this will also gradually reduce the chronic budget deficit incurred by NICUs. Finally, there

was a marked quantitative increase in bed capacity, with a total of 97 NICUs having a total of 1,866 beds, calculated as 4.6 beds per 1,000 annual live births, which meets the present need for NICU beds in Korea. (15) However, there continues to be a shortage of human resources and multi-disciplinary support systems for high-risk neonates. Governmental support for nationwide QI in NICUs needs to be addressed. Moreover, there needs to be not only a classification system of NICUs according to mandatory training requirements of the staff, skills, and equipment, but also the development of an efficient transfer system of high-risk pregnant women and neonates between different levels of NICU.

## IMPLEMENTATION OF THE KOREAN NEONATAL NETWORK

### Establishment of the KNN

An initial step in developing the KNN involved building a task force for reviewing and benchmarking other networks. A systematic process of weekly teleconferences, task force member meetings, and public hearings for the Korean Society of Neonatology members was implemented. After 4 months of preparation, the organizing committees were formed and the KNN was officially established on April 15, 2013. (16) The project “Construction and Operation of National Registry for the Development of Management Index of Very Low Birth Weight Infants in Korea,” was awarded funding by the KCDC.

Data of VLBW infants admitted to the NICU after birth or transferred from other hospitals to the KNN participating hospitals within 28 days after birth are entered in the KNN registry. VLBW infants who die in the delivery room or are transferred to a hospital outside the KNN within 28 days after birth are excluded. Moreover, each participating hospital is required to obtain institutional review board approval to participate in the KNN registry. Case registration requires informed consent from parents for the use of patient information.

As of August 2018, a total of 70 hospitals are currently participating in the KNN (Fig 1). Over 2,000 VLBW infants are registered annually, accounting for more than 70% of the total admissions of VLBW infants born in Korea. (5)

### System of the KNN

The electronic case report form (e-CRF) for KNN registration is based on the Internet-Based Clinical Research and Trial system of the KCDC and user training is mandatory. Data can be entered at any time from all KNN member

hospitals, and is immediately and confidentially stored in a de-identified format on the server of the KCDC.

An e-CRF consists of data from 3 visits:

- Visit 1: At discharge from the NICU
- Visit 2: Outpatient follow-up at 18 to 24 months of corrected age
- Visit 3: Outpatient follow-up at age 3 years

The e-CRF includes approximately 120 items for visit 1 and 70 items each for visits 2 and 3.

The KNN has a real-time data display system on the authorized member's page on their web site. The ranking of each participating hospital by 11 principal outcomes (eg, admission rate, follow-up rate, mortality, sepsis, necrotizing enterocolitis [NEC], bronchopulmonary dysplasia [BPD]) is displayed, with the names of other centers hidden using vertical bar charts with stacked numbers or average percentage (Fig 2A). Participating hospitals can compare their performance with those of other KNN participating hospitals, displayed by various types of charts in the same window. Conditional filtering tools for exclusive reviewing of the records of interest are provided in all charts. Users can choose any variable from the 144 outcome variables that are listed in the in-hospital and follow-up data as conditions for data filtering, and the statistical results of the outcome variables are then displayed on the HyperText Markup Language-based chart graphs and tables. (17) For example, Fig 2B displays the trend of mean base deficit in the blood gas analysis performed within the first hour after birth by year. Figure 2C depicts a horizontally stacked bar graph that displays the percentage of each category of respiratory support mode given at 28 days of age after conditional filtering. The vertical bar graphs in Fig 2D display the number of patients registered who were born at a specific gestational week after conditional filtering. Figure 2E depicts horizontal bar graphs that display the stacked number of annual hospitalizations of VLBW infants after conditional filtering. A few quantitative variables (eg, weight at 18 months' corrected age) in the e-CRF can be converted to categorical variables (eg, percentage of the corresponding percentile range) for chart display (Fig 2F). The graphs can be downloaded as files or can be printed for further use. Real-time data reporting facilitates further studies and QI, supporting network members through interactive analyses of the registered data.

Consistent and appropriate data management and monitoring are essential. The KNN has developed a query system when incorrect data are entered. It consists mainly of queries automatically generated by the e-CRF system, and a secondary query manually entered after periodic inspection by the central data manager. (16) In addition, a unique



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## Jeju (1)

Jeju National University Hospital

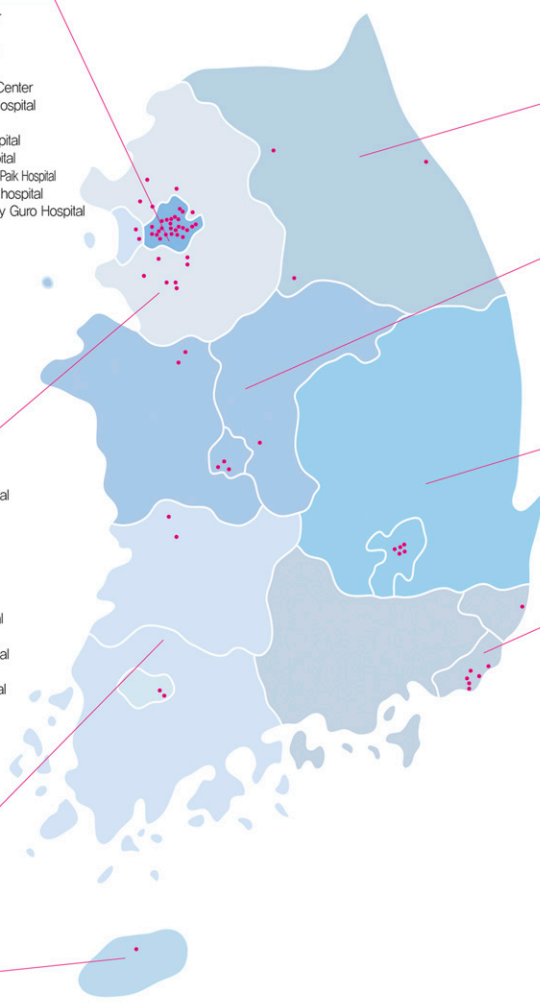


Figure 1. Distribution of participating hospitals. Available at: <http://www.knn.or.kr/index.jsp>.

site-visit monitoring system was devised; all KNN member hospitals receive biannual site-visit monitoring by 2 individuals, a KNN member neonatologist and a professional monitor. (18) During the monitoring visits, the neonatologist performs data verification for 5% to 10% of patients registered in the e-CRF by comparing predetermined source document verification items with the actual medical record. The professional monitor checks the completeness of the institutional review board documents and informed consent forms, and verifies the actual registration rate based on the admission data among all the VLBW infants born in the institution. If patients are excluded because of parental refusal of registration to the KNN or early death of the infant before consent is obtained, only basic demographic information such as mortality, sex, gestational age, and birthweight are collected separately. Site-visit monitoring not only contributes to assurance of data quality, but also

provides effective information through face-to-face training and exchange of ideas.

The KNN holds an educational seminar and a principal investigator seminar once a year. The KNN education subcommittee also provides educational activities through the KNN homepage, including a question-and-answer section with real-time feedback. The KNN publishes a newsletter biannually for announcing various events and data status, such as follow-up rates, data finalization rates, and error completion rates, as well as updating members about research findings.

## Data Registry

As of August 2018, a total of 70 hospitals were participating in the KNN, and a total of 12,152 VLBW infants have been registered to date, with over 2,000 VLBW infants being registered per year. The Table shows annual



**Figure 2.** Examples of real-time data display system on the Korean Neonatal Network web site. A. The ranking of each participating hospital by principal outcomes is shown with the names of other centers hidden using vertical bars with stacked numbers or average percentages. B. Broken line plots display the trend of a continuous variable, mean base deficit, in the blood gas analysis performed within the first hour after birth by year. C. Horizontal stacked bar graph displays the percentage of each category of respiratory support mode given at 28 days of age after conditional filtering. D. Vertical bar graph displays the number of patients registered according to gestational week after conditional filtering. E. Horizontal bar graph displays the percentage of annual hospitalizations of very-low-birthweight infants after conditional filtering. F. Horizontal stacked bar graph displays conversion from quantitative variables in the electronic case report form to categorical variables (eg, weight at 18 months of corrected age converted to the percentage of the corresponding percentile range). Available at <http://www.knn.or.kr/index.jsp> (accessible only to authorized members).

enrollment and major outcomes of VLBW infants registered in the KNN.

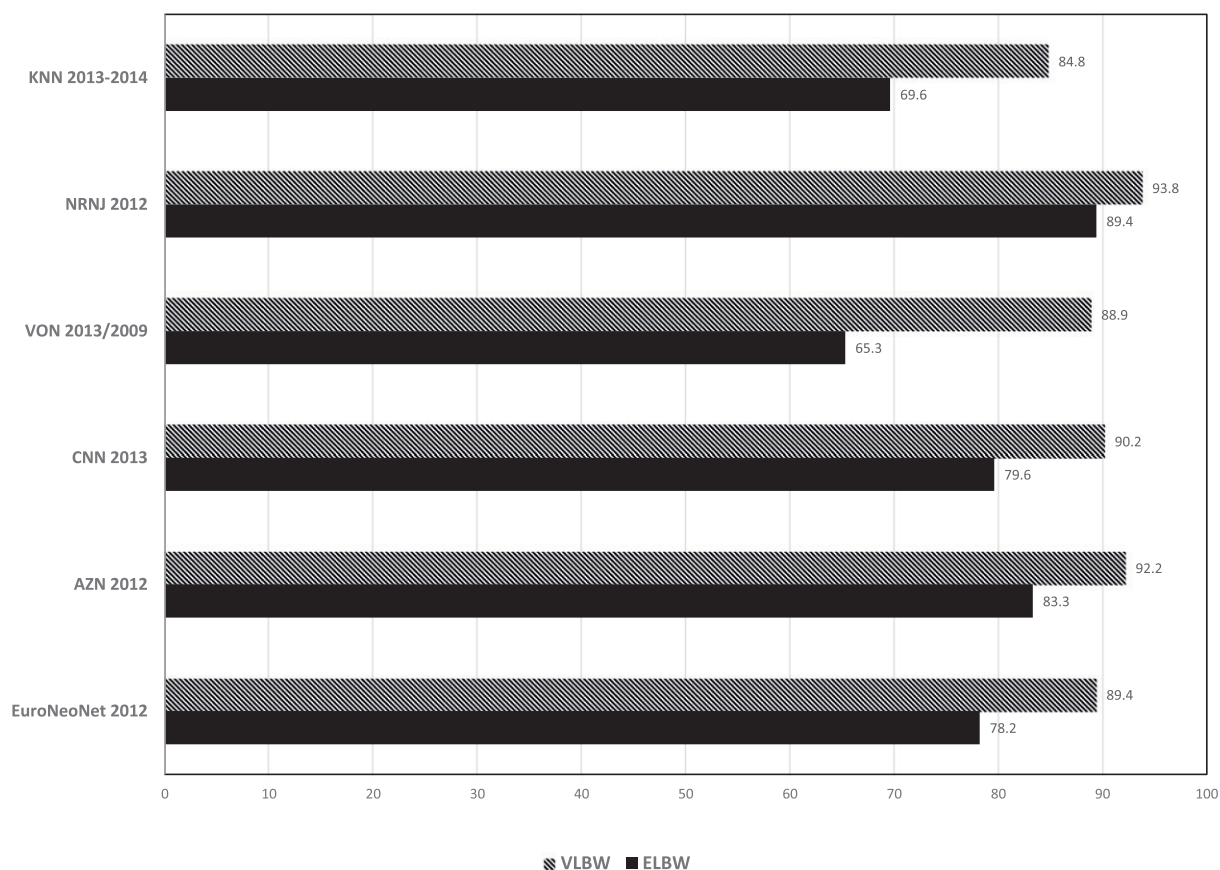
## OUTCOMES RESEARCH

Any investigator from the participating hospitals who has registered more than 10 patients in the KNN can apply to use the KNN data for research purposes at any time using an electronic application system on the KNN homepage. This research application system is managed by the ethics and publications subcommittee.

A recent study showed that the survival rate of VLBW infants in Korea has more than doubled from 35.6% in the 1960s to 84.8%, and the survival rate of extremely low-birthweight infants has increased more than 10-fold, suggesting a significant improvement in premature infant care. (19) When comparing VLBW infants among various networks, the survival rate of VLBW infants in Korea is close to that of the United States, but still lower than that of Japan (Fig 3). (9)

The identification of risk factors for mortality of VLBW infants is essential to the generation of prevention strategies to improve survival. In the first case-controlled multicenter study using KNN databases, the predominant causes of mortality in all infants born at 22 to 31 weeks of gestation were cardiorespiratory and neurologic complications, especially during the first week of age; this finding is consistent with the Italian and New South Wales and Australian Capital Territory-based cohort study. (20)(21)(22) In addition, mechanical ventilation for more than 2 weeks was confirmed as increasing the adjusted hazard ratio for mortality when compared with mechanical ventilation for 7 days or less. The individual mortality rate reached 50% at 14 weeks of cumulative mechanical ventilation. (23)

Hormonal, physiologic, and developmental differences between male and female infants are important because they can cause sex-specific outcomes such as mortality, respiratory distress syndrome, and BPD in preterm infants. (24) The risk of BPD and combined morbidities in VLBW infants born between January 2013 and December 2014 in



**Figure 3.** Comparison of the survival rate in very-low-birthweight infants and extremely low-birthweight infants among various networks. Data adapted from Shim et al. (9) AZN=Australia-New Zealand Neonatal Network; CNN=Canadian Neonatal Network; ELBW=extremely low-birthweight; EuroNeoNet=European Neonatal Network; KNN=Korean Neonatal Network; NRNJ=Neonatal Research Network of Japan; VLBW=very-low-birthweight VON=Vermont Oxford Network (35).

Korea was significantly higher in males born at less than or equal to 25 weeks of gestation (odds ratio [OR] 2.08, and OR 2.00, respectively). During the same period, the incidence of periventricular leukomalacia was significantly higher in male infants between 23 and 29 weeks of gestation. The risk of severe retinopathy of prematurity (ROP) was higher in female infants over 25 weeks of gestation. Although the risk of death was similar in both sexes, male sex has been identified as an independent risk factor for major morbidities, especially at less than 25 weeks of gestation. (25)

To promote postnatal growth and prevent associated adverse outcomes, efforts to optimize nutritional support in the NICU have increased in recent years. However, poor growth continues to be prevalent in the NICU setting. Growth failure, defined by a decrease in weight Z score between birth and discharge of more than  $-1.28$  using the Fenton growth charts, was assessed in the KNN database from 2013 to 2014. (26) Growth failure was observed in 45.5% of infants, with a rate of 68.9% in the small-for-gestational age group and 36.2% in the appropriate-for-gestational age group. (26) The Vermont Oxford Network (VON) has reported that the prevalence rate of discharge weight lower than the 10th percentile for postmenstrual age was 50.3% in 2013, and has been showing gradual improvement from 2000 to 2013. (27) In the California Perinatal Quality Care Collaborative, weight Z score falling above 1.0 between birth and discharge was found in 41%, and a weight below the 10th percentile for age at discharge was seen in 53%, with improvement in growth failure in the network over time. (28) The KNN study found that a delay in achieving 100 mL/kg per day of enteral feedings was a predictor of postnatal growth failure, and early initiation and aggressive progression of enteral nutrition was suggested in order to decrease the incidence of postnatal growth failure. (26)

There are diverse treatment strategies for a patent ductus arteriosus (PDA) in preterm infants, and the current management of PDAs in Korea was evaluated using a national cohort to establish a standardized treatment guideline. Data from the KNN showed that 46.5% of infants were diagnosed or treated for a PDA between 2013 and 2014. These infants were grouped based on management strategies for the PDA as follows: symptomatic treatment (56.9%), presymptomatic treatment (20.2%), conservative treatment (16.3%), and prophylactic treatment (6.5%). (29) Presymptomatic treatment of PDA involved treating asymptomatic infants who had either echocardiographic findings or increased B-natriuretic peptide levels that were indicative of the presence of a PDA. Prophylactic PDA treatment involved treating infants for a PDA when there were no clinical symptoms, diagnostic abnormalities on echocardiography, or increased B-natriuretic peptide levels. In our cohort, fewer infants received

prophylactic treatment and more infants received symptomatic as well as conservative treatment, when compared to other studies. (30)(31)(32) Although symptomatic treatment was still the most favored treatment in the group with GAs less than 24 weeks, conservative treatment was preferred more than any other treatment in the group with GAs greater than or equal to 32 weeks. According to a study of the Canadian Neonatal Network database, surgical ligation of a PDA in preterm infants was associated with increased neonatal mortality and/or morbidity. (32) In a single study from Korea, despite the longer duration of PDA exposure, nonintervention was associated with a significantly lower incidence of BPD, as well as no difference in mortality or morbidities such as NEC or intraventricular hemorrhage (IVH) when compared with a ductal closure strategy. (33)

The overall incidence of NEC ( $\geq$  stage 2) among VLBW infants born between January 2013 and June 2014 in Korea was noted to be 6.8%, with lower GA and birthweight being associated with a higher incidence of these morbidities, similar to that seen in other network studies (range 3%–11%). (34)(35)(36) Except for the lower GA, lower birthweight, and formula feeding, there is a lack of universal agreement on the importance of reported risk factors for NEC. (37) However, implementation of targeted interventions using modifiable risk factors has demonstrated decreases in the occurrence of NEC through QI projects. (38) In Korea, NEC was consistently associated with hypotension within 1 week after birth (OR 2.0). In the medical NEC group, lower GA was shown to have statistical significance, and in the surgical NEC group, an increased incidence of PDA was noted. (34)

Sepsis was found in 21.1% of VLBW infants born between January 2013 and June 2014 in the KNN. (39) Early-onset sepsis confirmed with a positive blood culture within 7 days after birth was found in only 3.6% of VLBW infants; however, the mortality rate was as high as 34.1%. Early-onset sepsis was associated with an increased risk of BPD and IVH. Most of the early-onset sepsis was caused by gram-positive organisms, particularly coagulase-negative *Staphylococcus* (30.6%). Late-onset sepsis, defined as the presence of bacteremia after 7 days after birth, occurred in 19.4% of VLBW infants with a 16.1% mortality rate between 2013 and 2014; the predominant organism identified was coagulase-negative *Staphylococcus* (38.3%). Because these rates are higher than those reported by the VON, efforts for QI are needed. Based on VON reports, it took 5 years before 75.0% of the NICUs achieved the shrunken adjusted rate from the best quartile for late-onset infection. (35) Of the first late-onset sepsis episodes, 25% and 50% occurred after 12 days and 20 days from birth, respectively. (35)



IVH was observed in 42.2% of VLBW infants born between 2013 and 2014 in the KNN, with IVH grades 1, 2, 3, and 4 in 25.1%, 7.0%, 4.8%, and 5.5% of infants, respectively. (40) The incidence of IVH grades 2 to 4 or grades 3 to 4 in infants born at 25 to 28 weeks' gestation in the KNN is similar to that observed in the Canadian Neonatal Networks, EuroNeoNet, and the US National Institute of Child Health and Human Development (NICHD); however, for infants of less than 24 weeks' gestation, the incidence appears to be higher. (41)(42)(43) Posthemorrhagic hydrocephalus developed in 0%, 3.5%, 36.1%, and 63.8% of the surviving infants with IVH grades 1, 2, 3, and 4, respectively. Only the severity of IVH was confirmed to be a risk factor for developing posthemorrhagic hydrocephalus in infants with IVH grades 3 to 4. (40)

The overall incidence of BPD was 28.9% of infants enrolled in the KNN, which is similar to that reported by VON, though it tended to be lower than the overall incidence reported in the NICHD study. (35)(44)(45) Among the limited data on VLBW infants between 2013 and 2014, the incidence of BPD increased by 85% (from 17.8% to 33.0%) and the mortality decreased by 31.4% (from 18.8% to 12.9%) compared to those in the study conducted in 2007 to 2008. The increased incidence of BPD with increasing survival rate of premature infants is consistent with findings of other studies. (35)(46) However, the rate of increasing BPD incidence was much higher than the rate of the decrease in mortality. Thus, further research is necessary to explain this gap.

The overall incidence of ROP was 34.1% between 2013 and 2014 in the KNN. Among the VLBW infants who underwent examination by an ophthalmologist, 11.6% were noted to have ROP at greater than or equal to stage 3 and 11.5% received treatment. (47) Interestingly, this study noted that the incidence of ROP among VLBW infants born after 31 weeks of gestation was 8.4%, including those with stage 3, emphasizing the importance of ROP screening in infants with even higher GA when indicated. Several studies have reported that lower GA and birthweight, maternal preeclampsia, anemia, septicemia, oxygen therapy, and mechanical ventilation were risk factors for ROP. (48) (49) In the KNN study, PDA (OR 2.1) and invasive ventilation duration (OR 1.0) were significant independent risk factors for ROP greater than or equal to stage 3.

## QUALITY IMPROVEMENT

Feedback of comparative, risk-adjusted outcome information through an individual annual report is important to support continuous QI efforts. However, though

information is necessary, by itself, it is not enough to promote continuous QI. The information needs to be interpreted and transformed into action. The KNN participating hospitals receive objective feedback comparing the current status of their NICUs with those of other KNN participating sites. They can analyze these data through the real-time display system at the KNN website, which is available at any time. (17) In addition, the KNN executive committee publishes an annual report using the data for all registered patients born in the previous year that have already been cleared through the data management process and locked. (16) The annual report provides a summary about all e-CRF items, especially some variables that are analyzed by 1-week GA and 100-g birthweight categories. Moreover, the KNN executive committee sends individual annual reports confidentially to each principal investigator from every institution. The report provides a comparison of important items such as major morbidity and mortality rates among all participating hospitals and individual hospitals, along with a summary of data analyzed by 1-week GA and 100-g birthweight categories.

The KNN recently initiated a multicenter QI project for improving neonatal sepsis. Among 70 KNN participating hospitals, 3 hospitals ranked in the upper 25th percentile and 1 ranked in the lower 10th percentile in late-onset sepsis rate based on the KNN registry data. After obtaining permission from the hospitals, they enrolled as QI participating hospitals and benchmarking hospitals. The QI team from each participating hospital set up its own QI strategies based on evidence-based protocols suggested by peer reviewers in the KNN, such as central line-associated bloodstream infection control, indwelling catheter use, antibiotic use, and proper use of newly introduced products, including needleless connectors. Visits were made to the benchmarking hospital to learn effective ways to perform the strategies. The incidence of late-onset sepsis, as the main QI measure, is currently being collected by the KNN, and regular monitoring with feedback is being provided to participating hospitals. Because this 2-year QI project uses currently existing KNN data variables, ongoing evidence-based practices can be applied simultaneously to multiple institutions, and the effect of the various interventions can be determined in real time.

## FUTURE STEPS

### Infrastructure for Neonatal Multicenter Clinical Research

The KNN aims to provide an infrastructure for multicenter, randomized, clinical trials to validate the effectiveness of new treatment and management policies in high-risk

newborns in Korea. Multicenter clinical trials can promote scientific development and improve the care delivered to high-risk infants, thus resulting in improved survival through the development of new neonatal intensive care policies that are appropriate in our health-care environment.

### Specific High-Risk Newborn Registries

The KNN plans to expand the registries for specific high-risk newborns, such as the National Therapeutic Hypothermia Registry. The number of infants treated with therapeutic hypothermia for hypoxic-ischemic encephalopathy in Korea has been increasing; however, neurologic sequelae persist. The KNN also plans to include a follow-up registry to assess the long-term neurodevelopmental outcomes in late preterm compared with term infants. Through the

establishment of a specific targeted registry, it will be easier to collect data on the current status of high-risk infants, and work towards implementing better practice strategies for quality improvement.

### Global Impact via Internetwork Comparisons

The International Network for Evaluation of Outcomes is a collaboration among an international group of neonatal networks that performs research on the management and outcomes of extremely preterm and extremely low-birth-weight neonates. (50) The network maintains a standardized NICU database and aims to improve the efficacy and efficiency of neonatal care. Eventually, by joining this group, improvements in quality of life can be a universal international goal aimed at increasing survival rates of high-risk

TABLE. Annual Enrollment and Major Outcomes of Infants Born Between 2013 and 2016 and Enrolled in the KNN

VARIABLE	2013	2014	2015	2016
Hospitals	49	55	60	66
Number of VLBW infants (visit 1)	1398	2128	2400	2365
(visit 2)			1000	1660
(visit 3)				1113
Mortality type I <sup>a</sup>	10.0%	15.1%	13.9%	15.4%
Mortality type II <sup>b</sup>	11.4%	16.6%	13.6%	15.4%
RDS	77.0%	79.4%	79.5%	76.2%
BPD (≥ moderate)	34.9%	28.6%	28.0%	29.2%
PDA ligation	12.2%	12.2%	9.7%	9.6%
IVH (≥ grade 2)	16.7%	18.7%	17.2%	17.1%
NEC (≥ stage 2)	7.4%	6.2%	6.1%	7.3%
Sepsis	21.7%	21.4%	19.8%	20.8%
PVL	10.9%	8.3%	6.9%	6.7%
ROP (≥ stage 2)	24.5%	22.7%	20.6%	19.8%
Cerebral palsy at 18–24 months corrected age			6.6%	6.2%
Blindness at 18–24 months corrected age			0.7%	0.5%
Deafness at 18–24 months corrected age			2.8%	1.9%
Cerebral palsy at 36 months of age				8.4%
Blindness at 36 months of age				0.3%
Deafness at 36 months of age				2.9%

BPD=bronchopulmonary dysplasia; IVH=intraventricular hemorrhage; KNN=Korean Neonatal Network; NEC=necrotizing enterocolitis; PDA=patent ductus arteriosus; PVL=periventricular leukomalacia; RDS=respiratory distress syndrome; ROP=retinopathy of prematurity.

<sup>a</sup>Type I mortality: mortality in registered cases only.

<sup>b</sup>Type II mortality: mortality in registered and unregistered cases (patients who met the inclusion criteria for the KNN registry but were not registered were surveyed about their gestational age, birthweight, and outcome during the process of KNN data monitoring).



neonates, decreasing risks of major complications and socioeconomic burden, and increasing the proportion of the productive economic population.

## CONCLUSION

The introduction and implementation of the KNN has played an important role in sharing data and ultimately standardizing practice, and has already shown substantial benefits in improving neonatal outcomes in a relatively short amount of time. In addition, the KNN has positioned itself as a powerful tool for both research and QI processes. Efforts toward improving international standards and evidence-based medicine through network-based multicenter clinical trials will be necessary in the future.

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## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the issues in the organization of perinatal care (eg, regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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**International Perspectives: Implementation of the Korean Neonatal Network**  
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# Prevention of Bronchopulmonary Dysplasia: A Summary of Evidence-Based Strategies

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## Education Gap

To decrease rates of bronchopulmonary dysplasia among extremely preterm infants, clinicians must implement multiple evidence-based strategies that target disease prevention. Less invasive surfactant administration is an emerging therapy that may help prevent bronchopulmonary dysplasia.

## Abstract

Bronchopulmonary dysplasia (BPD) is the most common chronic complication associated with extremely preterm birth. Although BPD is now an uncommon condition in infants born with birthweights higher than 1,500 g, among infants born at or near the current limits of viability, BPD rates have not improved over the past 2 to 3 decades and may be increasing. No single therapeutic intervention is effective at preventing BPD. As such, clinicians must use multiple evidence-based strategies to help reduce BPD rates. This review examines current evidence-based approaches to BPD prevention, primarily focusing on data obtained from randomized controlled trials.

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### ABBREVIATIONS

BPD	bronchopulmonary dysplasia
CI	confidence interval
CP	cerebral palsy
CPAP	continuous positive airway pressure
HFNC	high-flow nasal cannula
HFOV	high-frequency oscillatory ventilation
INSURE	intubation, surfactant administration during brief mechanical ventilation followed by extubation
LISA	less invasive surfactant administration
NEC	necrotizing enterocolitis
NIPPV	nasal intermittent positive pressure ventilation
OR	odds ratio
PDA	patent ductus arteriosus
RCT	randomized controlled trial
RDS	respiratory distress syndrome
RR	relative risk

## Objectives After completing this article, readers should be able to:

1. Describe current evidence-based therapies shown in randomized controlled trials to reduce bronchopulmonary dysplasia risk among very preterm infants.
2. Become familiar with the data available on the safety and efficacy of corticosteroids for preventing bronchopulmonary dysplasia in extremely preterm infants and explain the current limitations in knowledge about the optimal timing, dosing regimen, and patient selection for treatment.

## INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most common complications of preterm birth. It affects approximately half of all infants born with birthweights less than 1,000 g, is associated with increased risk for early childhood mortality, and predisposes survivors to chronic respiratory and cardiovascular impairments,



growth failure, and neurodevelopmental delay. (1)(2)(3)(4)(5) (6)(7) BPD was once a frequent problem among all preterm infants treated with prolonged invasive mechanical ventilation. With increased use of antenatal corticosteroids, surfactant therapy, and gentle ventilation strategies, BPD is now uncommon in preterm infants born with birthweights greater than 1,500 g. (8) However, most of the data available suggest that BPD rates have not improved in recent decades among extremely preterm infants and may be increasing. (7) (8)(9)(10) One hindrance to preventing BPD in this population is the lack of a safe and highly efficacious preventive therapy. As such, clinicians must use multiple evidence-based strategies to reduce BPD risk. This review discusses the evidence supporting currently available therapies for BPD prevention in very preterm infants, primarily focusing on data obtained from randomized controlled trials (RCTs).

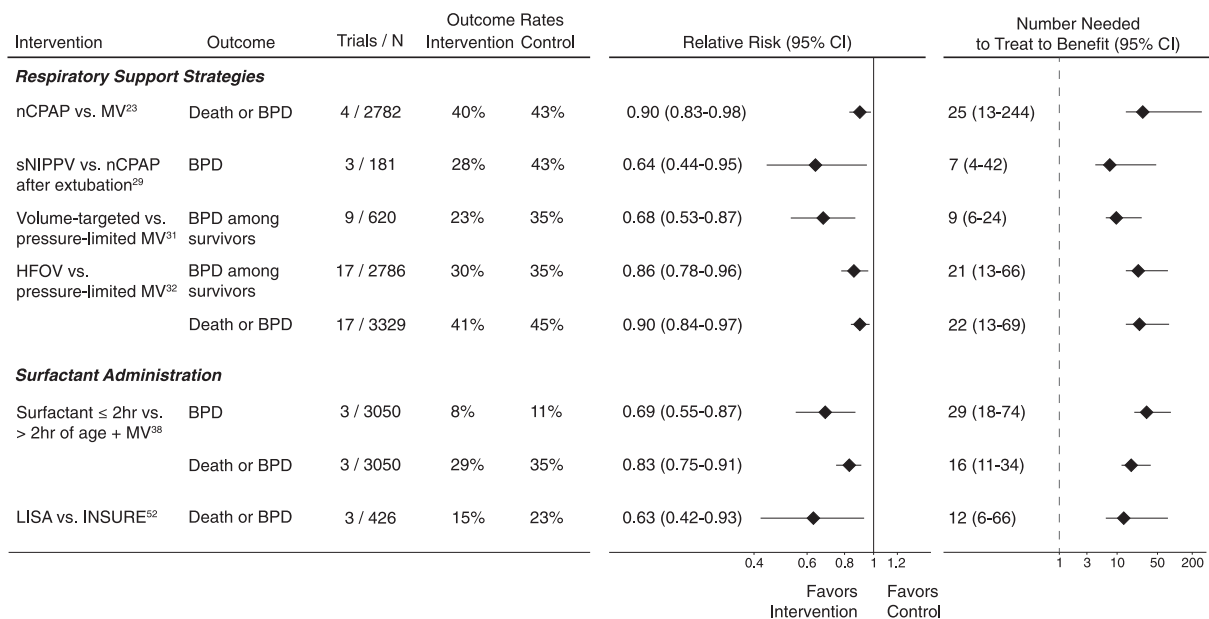
## RESPIRATORY SUPPORT STRATEGIES

Successful transition to postnatal breathing requires clearance of fetal lung fluid and lung aeration. The high chest wall compliance, weak respiratory muscles, incomplete surfactant production, and underexpression of transepithelial sodium channels in very preterm infants hinder this process. (11)(12)(13)(14) As a result, many very preterm infants require positive airway pressure and supplemental

oxygen soon after birth to maintain physiologic stability. Invasive mechanical ventilation can be lifesaving in these instances, but it may also lead to lung injury. Animal data show a clear link between baro- and volutrauma induced by mechanical ventilation and pathologic changes in the lung that mimic BPD. (15)(16) Moreover, observational studies support an association between invasive mechanical ventilation and increased BPD risk. (17)(18) To help minimize lung injury and prevent BPD, investigators have explored several different noninvasive and “gentler” invasive ventilation strategies. Salient results from these efforts are described herein; data from RCTs showing benefit for BPD prevention are summarized in Fig 1.

### Noninvasive Positive Airway Pressure

One strategy to prevent ventilator-induced lung injury is to avoid mechanical ventilation altogether. Three large RCTs compared early noninvasive continuous positive airway pressure (CPAP) with immediate intubation and surfactant administration. (19)(20)(21) Although design elements, including gestational ages of the enrolled infants and initial CPAP settings (ranging from 5–8 cm H<sub>2</sub>O) varied among the studies, each demonstrated a nonsignificant reduction in the rate of death or BPD at 36 weeks’ postmenstrual age among the infants initially treated with CPAP. (19)(20)(21) Meta-analyses of the available trial data, some of which also



**Figure 1.** Summary of randomized, controlled trial data on the effects of various respiratory support strategies for preventing death and/or bronchopulmonary dysplasia. Study results are abstracted from the cited publication when available. If not provided in the article, relative risk and number needed to treat to benefit values (inverse of the risk difference) were calculated using original study data in RevMan version 5.3 (the Nordic Cochrane Centre, Copenhagen, Denmark). BPD=bronchopulmonary dysplasia; CI=confidence interval; HFOV=high-frequency oscillatory ventilation; INSURE=intubation, surfactant administration during brief mechanical ventilation, followed by extubation; LISA=less invasive surfactant administration; MV=mechanical ventilation; N=total number of infants evaluated for the outcome; nCPAP=nasal continuous positive airway pressure; sNIPPV=synchronized nasal intermittent positive pressure ventilation.

included smaller RCTs, showed a small but statistically significant reduction in the risk for death or BPD with CPAP therapy (Fig 1). (22)(23)(24) Although one large trial reported higher rates of pneumothorax in CPAP-treated infants, (20) meta-analyses did not show an increased risk for pneumothorax or other adverse events with early CPAP. (22)(23)(24) As a result, the American Academy of Pediatrics Committee on Fetus and Newborn recommends early use of CPAP with subsequent selective surfactant administration in extremely preterm infants as an evidence-based strategy to reduce the risk for death or BPD. (25)

Heated and humidified high-flow nasal cannula (HFNC), typically administered with flow rates higher than 1 to 2 L/min, has gained popularity as an alternative to nasal CPAP. Potential advantages of HFNC include reduced nasal trauma, simpler device setup, and greater facilitation of oral feeding and skin-to-skin care. (26) However, recent trial data indicate that HFNC and nasal CPAP may not be equivalent therapies. Treatment failure is more common among very preterm infants who receive HFNC compared with nasal CPAP as a primary support modality. (26) HFNC may be an acceptable alternative to nasal CPAP for postextubation support among infants born at more than or equal to 28 weeks of gestation, but routine use in less mature infants is not recommended. (27)

Nasal intermittent positive pressure ventilation (NIPPV) augments nasal CPAP by providing brief periods of higher airway pressure, synchronized with an infant's breathing or delivered at set, asynchronous intervals. Use of NIPPV in preterm infants as an initial mode of respiratory support or after extubation from mechanical ventilation, when compared with CPAP, results in improved short-term respiratory outcomes without an increased risk of harm. (28)(29) Despite this benefit, meta-analyses do not show a reduction in BPD with NIPPV. (28)(29) Synchronized NIPPV, particularly when used after extubation, may reduce BPD risk (Fig 1), but further research into the usefulness of this specific form of noninvasive support is needed. (29)

### Mode of Invasive Mechanical Ventilation

Not all very preterm infants safely transition to postnatal breathing with noninvasive respiratory support. Data from CPAP trials indicate that up to 65% of spontaneously breathing extremely preterm infants require intubation and mechanical ventilation despite early CPAP therapy. (23) In these instances, or when invasive respiratory support is required soon after birth, clinicians must select a mode of mechanical ventilation. Trauma to the developing lung from excessive volumetric stretch is one proposed contributor to the development of BPD. (30) Owing to rapid changes in

lung compliance in the first days and weeks after birth, volume-targeted ventilation in very preterm infants may be optimal. A 2017 Cochrane review found moderate quality of evidence supporting the use of volume-targeted ventilation as opposed to pressure-limited ventilation as a means to reduce the composite outcome of death or BPD, length of mechanical ventilation, and rates of severe intraventricular hemorrhage (Fig 1). (31)

High-frequency oscillatory ventilation (HFOV) is an alternative ventilation strategy that may reduce lung injury. A 2015 Cochrane review evaluating HFOV as a primary mode of invasive respiratory support (ie, not as a rescue therapy after "failed" conventional mechanical ventilation) found a small reduction in the risk for death or BPD and BPD alone among infants treated with HFOV compared with pressure-limited conventional ventilation (Fig 1). (32) Pulmonary air leaks (pneumothorax or pulmonary interstitial emphysema) were more common in HFOV-treated infants. (32) Ultimately, the authors concluded that the "preference for a specific ventilation mode remains a matter of clinical judgment requiring a balance between a relatively small benefit and a possible short-term harm." (32)

## SURFACTANT

### Endotracheal Surfactant Administration Followed by Mechanical Ventilation

Endogenous pulmonary surfactant is a mixture of lipids and proteins that primarily act to reduce surface tension at the air/liquid interface within the alveoli and improve deflation stability of the lungs. (33) Deficiency of pulmonary surfactant in extremely preterm infants is a key component in the pathophysiology of neonatal respiratory distress syndrome (RDS). (34) Several older RCTs, conducted before the routine use of antenatal corticosteroid and early noninvasive CPAP, showed that administration of exogenous surfactant, compared with mechanical ventilation alone, reduced rates of death or supplemental oxygen use 28 days after delivery (the standard definition of BPD at that time). (35)(36)(37) As described herein, use of noninvasive respiratory support as a primary modality is the preferred approach for most very preterm infants. However, these older trial data support the use of exogenous surfactant in very preterm infants who require intubation and mechanical ventilation within the first 48 to 72 hours of age. In these instances, early treatment with surfactant may be optimal. Rescue surfactant administration to preterm infants receiving mechanical ventilation within the first 2 hours of age, compared with after the second hour of age, reduces the risk for BPD and the composite risk for death or BPD (Fig 1). (38)

There are several commercially available surfactant formulations available for use. The animal-derived preparations (modified or purified from bovine or porcine lungs) provide a small benefit for reductions in rates of mortality and death or BPD compared with first-generation protein free surfactants. (39) Meta-analysis of trials comparing modified bovine-derived surfactant to porcine-based surfactant suggested that bovine products may increase mortality and BPD risk. (40) However, subgroup analyses suggested that these differences were limited to trials using a higher initial dose of porcine-derived surfactant and may not be due to the animal source. (40) Lucinactant, a second-generation synthetic surfactant that contains a peptide analog of surfactant protein B, has similar efficacy as animal-derived products. (41)(42)

### Surfactant Administration without Prolonged Mechanical Ventilation

To maximize the potential benefits of early surfactant administration without the harmful effects of prolonged invasive mechanical ventilation, investigators explored alternative means to dosing surfactant. Victorin et al introduced the technique of *intubation, surfactant administration during brief mechanical ventilation, followed by extubation* (INSURE). (43) Although initial RCTs found that INSURE reduced supplemental oxygen use at 28 days of age, meta-analyses including more recent trials found that compared with CPAP, INSURE does not reduce the risk for death or BPD (relative risk [RR] 0.88, 95% confidence interval [CI] 0.76–1.02). (44)(45)

Several techniques have been developed for less invasive administration of surfactant to avoid standard endotracheal intubation. These include intratracheal instillation of surfactant with a thin catheter (eg, nasogastric tube), aerosolized surfactant, intrapartum pharyngeal instillation, and delivery via a laryngeal mask airway. (46) Of these strategies, surfactant instillation via a thin catheter, typically referred to as less invasive surfactant administration (LISA) or minimally invasive surfactant therapy, is the most studied. Four RCTs conducted in extremely preterm infants compared LISA with endotracheal tube administration of surfactant (3 versus INSURE, 1 versus continued mechanical ventilation after surfactant therapy), (47)(48)(49)(50) and 1 compared LISA with CPAP therapy alone. (51) A meta-analysis combining data from these RCTs showed that LISA versus control therapy reduced the risk for BPD among survivors (RR 0.70, 95% CI 0.50–0.97) and the composite of death or BPD (RR 0.74, 95% CI 0.58–0.94). (52) Compared with INSURE alone, LISA reduced the risk for death or BPD (Fig 1) but not BPD among survivors (RR 0.65, 95% CI 0.35–1.19). (52)

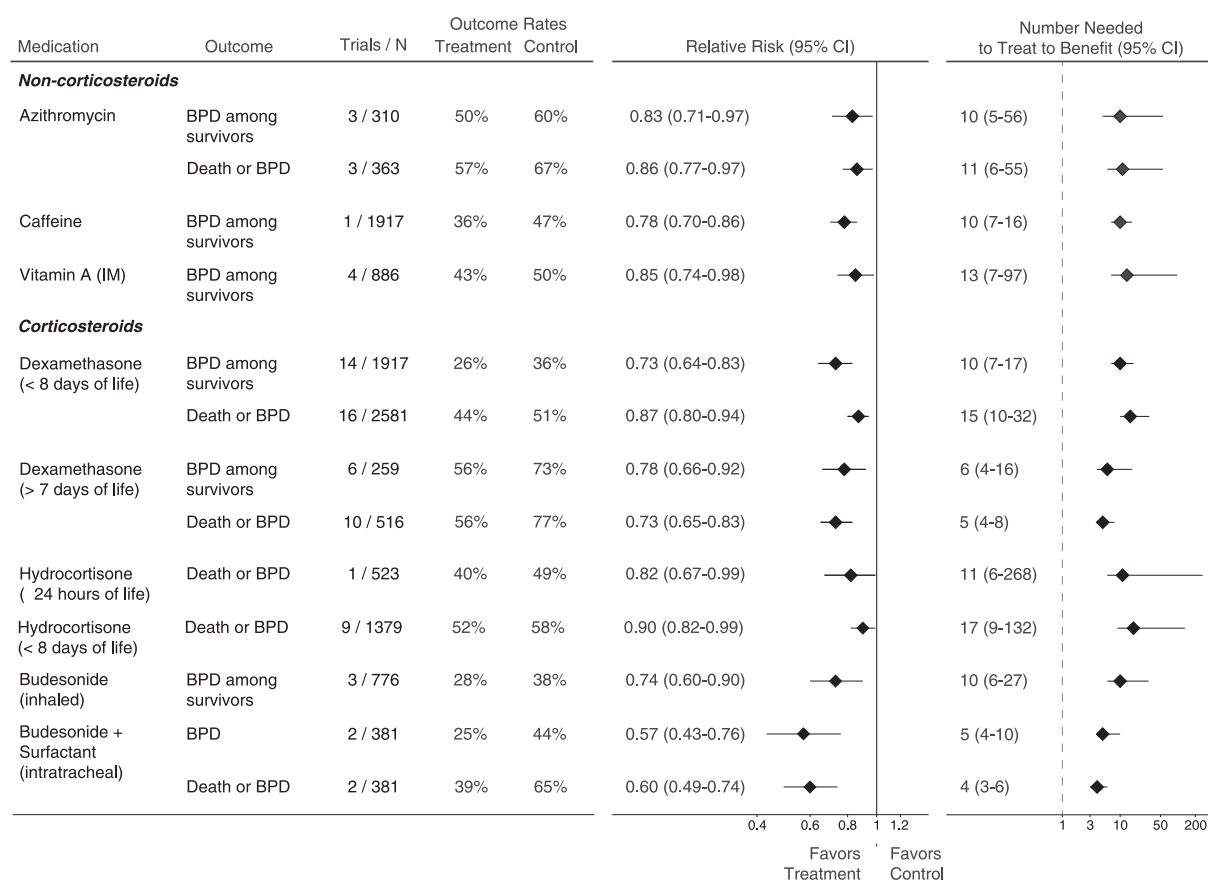
Isayama et al conducted a recent Bayesian network meta-analysis comparing 6 early respiratory strategies (mechanical ventilation, nasal CPAP, noninvasive positive pressure ventilation, INSURE, LISA, and nebulized surfactant administered via laryngeal mask airway). (53) This approach estimated the relative effects of each intervention, even if they were not compared in individual trials. The analysis showed that LISA was associated with the largest reduction in the risk for death or BPD (odds ratio [OR] 0.49, 95% CI 0.30–0.79). (53) However, the authors noted that the findings were limited by the overall low quality of evidence. (53) A large, ongoing trial evaluating LISA in extremely preterm infants will provide important data on this method of surfactant administration. (54)

## PHARMACOLOGIC THERAPIES

Despite the strong physiologic and observational data implementing invasive mechanical ventilation in the development of BPD, the beneficial effects of the respiratory support strategies described herein are modest. Longitudinal data also suggest that increased use of noninvasive respiratory support over time has not been accompanied by substantial improvements in BPD rates or childhood lung function among surviving extremely preterm infants. (55) Owing to the limited benefit of gentle ventilation techniques, pharmacologic therapies are an essential component in ongoing efforts to reduce BPD rates. Drug therapies shown in RCTs to reduce BPD are summarized herein and in Fig 2.

### Noncorticosteroid Agents

**Azithromycin.** Azithromycin is a macrolide antibiotic that exhibits both antimicrobial and anti-inflammatory properties. (56)(57) These dual qualities make it a potentially appealing mode of BPD prevention. In very preterm infants, infection with *Ureaplasma* is associated with the development of BPD. (58)(59) Moreover, lung and systemic inflammation contribute to BPD pathophysiology. (60)(61) Three small trials assessed the efficacy of azithromycin in preventing BPD. (62) A meta-analysis of these studies found a reduction in the risk for BPD and death or BPD alone among infants treated with azithromycin (Fig 2), regardless of known *Ureaplasma* colonization or infection. (62) However, none of the individual studies demonstrated benefit, and the quality of evidence was low. (62)(63) Finally, trials evaluating other macrolides have not shown benefit for preventing BPD. (64)(65) Larger trials are needed to establish safety and efficacy of prophylactic azithromycin before recommending this therapy. (63)



**Figure 2.** Summary of randomized, controlled trial data on the effects of various medications for preventing death and/or bronchopulmonary dysplasia. Study results are abstracted from the cited publication when available. If not provided in the article, relative risk and number needed to treat to benefit values (inverse of the risk difference) were calculated using original study data in RevMan version 5.3 (the Nordic Cochrane Centre, Copenhagen, Denmark). BPD=bronchopulmonary dysplasia; CI=confidence interval; IM=intramuscular.

**Caffeine.** Caffeine is approved by the US Food and Drug Administration for the treatment of neonatal apnea among infants born with gestational ages from 28 weeks to less than 33 weeks. The Caffeine for Apnea of Prematurity trial showed that caffeine also reduced BPD risk among infants with birthweights of 500 to 1,250 g and improved neuro-developmental outcomes at 18 to 21 months' corrected age (Fig 2). (66)(67) Follow-up trial data collected through age 11 years indicated that caffeine resulted in durable, long-term improvement in motor function. (68) Recent neonatal studies showed that beginning caffeine therapy within the first 72 hours of age may result in the greatest reduction in BPD risk. (69)(70)(71)(72)(73) Importantly, it is uncertain whether these findings are indicative of a true benefit of early caffeine or greater illness severity among the infants treated with caffeine beginning at later ages. Although further studies are needed to evaluate the risks and benefits of very early caffeine therapy, particularly among extremely preterm infants receiving invasive mechanical ventilation, use of caffeine soon after birth in most extremely preterm infants is recommended. (63)

**Vitamin A.** Vitamin A is required for the growth and maturation of epithelial cells lining the respiratory tract. (74) (75) Earlier studies showed that preterm infants who developed BPD, compared with those who did not, had lower plasma vitamin A levels. (76)(77)(78) Subsequently, a large, multicenter trial published in 1999 found that intramuscular injections of vitamin A during the first 4 weeks of age reduced rates of death or BPD and BPD alone among surviving extremely low-birthweight infants. (79) Meta-analysis of all trial data confirmed a small benefit for reducing BPD among survivors (Fig 2) but not for the composite outcome of death or BPD (RR 0.90, 95% CI 0.81–1.01). (80) More recent observational studies call into question the true effectiveness of vitamin A in the current era. One large study showed similar rates of BPD among infants who received vitamin A and untreated controls whereas another found that BPD rates remained stable during a vitamin A shortage in the United States, despite a precipitous drop in use of the supplement. (81)(82) An ongoing RCT investigating enteral vitamin A may help resolve the conflict between the trial and observational data. (83) However, in

the absence of these results, intramuscular vitamin A is recommended, if commercially available, as an evidence-based strategy to prevent BPD in extremely preterm infants.

### Corticosteroids

The potent anti-inflammatory properties of corticosteroids make them a logical therapeutic agent for BPD prevention. Unfortunately, the potential for long-term harm with corticosteroids and deficiencies in the available trial data, including variability in study design and frequent open-label steroid use among randomized infants, hinder the ability to determine the true risks and benefits of postnatal corticosteroids in very preterm infants.

**Dexamethasone (Systemic).** Of all corticosteroids, the use of dexamethasone to prevent BPD has been studied in the largest number of RCTs. Owing to differences in risk profile, meta-analyses incorporating these trials typically group studies evaluating dexamethasone initiated within the first 8 days of age (“early use”) separately from those initiating therapy after this time point (“late use”). The most recent Cochrane review on early dexamethasone therapy found that although use within the first 8 days after birth reduced BPD risk (Fig 2), it increased the risks for gastrointestinal perforation, hypertrophic cardiomyopathy, cerebral palsy (CP), and major neurosensory disability. (84) Because of these unacceptable side effects, early dexamethasone for BPD prevention is not recommended.

The risks and benefits of “late” dexamethasone are less well-established. Meta-analysis of the available trial data shows that initiation of dexamethasone after the first week of age reduces BPD risk (Fig 2), but carries the short-term side effects of hyperglycemia, glycosuria, and hypertension. (85) In contrast to early use, a recent meta-analysis did not find clear evidence of increased CP risk among surviving infants treated with late dexamethasone. (85) However, none of the follow-up studies were adequately powered to evaluate long-term outcomes, and the high rates of open-label dexamethasone use in these studies may mask actual treatment effects. (85)(86)

Ultimately, clinicians considering whether to administer “late” dexamethasone to individual infants must balance the medication’s beneficial respiratory effects with the potential adverse effects on long-term neurodevelopment. An important component in this calculus is the recognition that BPD is itself a risk factor for poor neurologic outcomes. (87)(88) A meta-regression conducted by Doyle et al provides the best means for clinicians to balance these competing risks. (88) This study showed that when the risk for BPD in the control population (akin to an infant’s baseline BPD risk) was less than 33%, corticosteroids significantly increased the risk for death or CP. (88)

Alternatively, when the risk for BPD exceeded 60%, corticosteroids reduced death or CP risk. (88) Therefore, in infants at low to moderate risk for BPD, the adverse long-term effects of dexamethasone likely outweigh the benefits. Conversely, among infants at high risk, the balance may favor dexamethasone therapy.

If a clinician decides to administer dexamethasone, he/she must then select a dose and treatment duration. Although general consensus favors the use of low, tapering doses administered for short periods (1–2 weeks at most), robust data to guide these specific choices are limited. (89) The dosing regimen used in the discontinued Dexamethasone: A Randomized Trial (DART) study (0.89 mg/kg administered over 10 days) is one such approach. (90) In this trial of 70 very preterm infants receiving invasive mechanical ventilation, compared with placebo, dexamethasone significantly improved rates of successful extubation (dexamethasone group 60%, placebo group 12%) without evidence of long-term harm. (90)(91) However, the risk for BPD was not significantly reduced in the dexamethasone-treated infants (OR 0.58, 95% CI 0.13–2.66). (90)

**Hydrocortisone (Systemic).** To date, 9 trials have evaluated the safety and efficacy of systemic hydrocortisone initiated in the first week after birth for prevention of death or BPD. (84) The largest of these studies, the PREMILOC trial, compared a 10-day course of low-dose hydrocortisone initiated within the first 24 hours after birth with placebo in infants born at less than 28 weeks’ gestation. (92) Rates of survival without BPD were higher among the hydrocortisone-treated infants (Fig 2). (92) However, a subgroup analysis demonstrated a nearly 2-fold increase in the risk for late-onset sepsis among infants born at 24 to 25 weeks’ gestation treated with early hydrocortisone. (92) Hydrocortisone also did not improve 2-year neurodevelopmental outcomes despite a reduction in death or BPD. (93) Meta-analysis of all available trials initiating hydrocortisone in the first week of age showed a reduction in the composite outcome of death or BPD with hydrocortisone therapy (Fig 2) but no benefit for BPD among survivors. (84) Gastrointestinal perforation was more common in the hydrocortisone-treated infants. (84) A recently completed RCT conducted in the US Neonatal Research Network evaluating the safety and efficacy of hydrocortisone administered to preterm infants receiving invasive mechanical ventilation at 14 to 28 days will provide additional safety and efficacy data.

**Budesonide (Inhaled).** Inhaled corticosteroids offer the potential benefit of reducing inflammation in the lung without the adverse side effects of systemically administered corticosteroids. The efficacy of 4 different inhaled steroids (budesonide, beclamethasone, fluticasone, flunisolide) for preventing BPD has been studied in RCTs. (94)(95)



A meta-analysis of all trial data (inclusive of all 4 steroids) demonstrated a reduced BPD risk among surviving infants (RR 0.76, 95% CI 0.63–0.93) and the composite outcome of death or BPD (RR 0.86, 95% CI 0.75–0.99) among infants treated with inhaled corticosteroids. (94) These beneficial findings are primarily driven by the multicenter NEUROSIS trial, which found that inhaled budesonide decreased rates of BPD among survivors (Fig 2), but at the expense of greater mortality among budesonide-treated infants. (96)(97) Rates of neurodevelopmental impairment at 18 to 22 months' corrected age were similar between the 2 study groups. (97) Although no etiology has been identified for the higher mortality in the budesonide group, this concerning finding outweighs the observed benefit for BPD. (97)

Two RCTs evaluated the usefulness of intratracheal budesonide combined with surfactant relative to surfactant therapy alone among very-low-birthweight infants with severe RDS. (98) The combined therapy reduced the risk for death or BPD (Fig 2). (98) Follow-up performed up to 3 years of age found no difference in motor or cognitive function between the groups. (98) This promising finding awaits confirmation in larger trials before widespread use is recommended.

## INEFFECTIVE OR UNPROVEN THERAPIES FOR BPD PREVENTION

Multiple medications and care strategies that are potentially useful for BPD prevention have ultimately been shown in RCTs to not reduce BPD risk. Although review of each of these therapies is outside the scope of this article, a few of the more common strategies warrant discussion.

### Antenatal Corticosteroids

Administration of antenatal corticosteroids to pregnant women at 23 to 33 6/7 weeks' gestation who are at increased risk for preterm delivery within the subsequent week is an evidence-based strategy to reduce neonatal morbidity and mortality. Meta-analysis of available trial data indicate that premature infants of women treated with antenatal steroids are at significantly reduced risk for developing neonatal RDS, intraventricular hemorrhage, necrotizing enterocolitis (NEC), and early-onset sepsis. (99) Despite these benefits, antenatal steroids have not been shown to reduce the risk for BPD in RCTs (RR 0.86, 95% CI 0.42–1.79) or large observational studies. (99)(100)

### Treatment of a Patent Ductus Arteriosus

Observational data demonstrate a strong association between the presence of a patent ductus arteriosus (PDA)

and the development of BPD. (101)(102) Despite this evidence, no medication that targets ductal closure (indomethacin, ibuprofen, acetaminophen) administered prophylactically or after identification of a "hemodynamically significant" PDA has been shown to reduce BPD risk. (103)(104)(105)(106)(107) Surgical ligation effectively achieves closure of the PDA, but may increase the risk for BPD and long-term neurodevelopmental impairment. (108)(109) Although it is possible that some very preterm infants may benefit from medical or interventional closure of the PDA, there are no evidence-based strategies to reliably identify these infants and then select the optimal therapeutic approach.

### Fluid Restriction and Diuretics

Excessive fluid intake may result in pulmonary edema and need for greater respiratory support. Observational data indicate that extremely low-birthweight infants who receive higher fluid intake and those with less robust weight loss in the first 1 to 2 weeks of age more commonly develop BPD. (102) However, the limited trial data do not show clear benefit with restrictive versus more liberal fluid administration. (110) Diuretics may reduce pulmonary edema and provide short-term improvement in respiratory mechanics in preterm infants but there are no data indicating reduced BPD risk with regular diuretic use. (111)

### Inhaled Nitric Oxide

Inhaled nitric oxide is a potent pulmonary vasodilator and an effective treatment for persistent pulmonary hypertension in near-term and full-term newborns. (112) Despite these benefits, inhaled nitric oxide does not prevent BPD when used as an early routine strategy or as a rescue therapy in very preterm infants. (113)(114) A recent individual patient meta-analysis using data from a subset of trials suggested that inhaled nitric oxide may reduce BPD risk among black preterm infants. (115) This promising finding requires validation in future studies.

### Breast Milk

Mother's own milk is the preferred source of enteral nutrition for most very preterm infants. In addition to being associated with reduced risk of developing NEC and late-onset sepsis, observational studies suggest that preterm infants who receive an exclusive diet of the mother's own milk as compared to preterm formula are less likely to develop BPD. (116)(117) Donor human milk is gaining popularity as an alternative to preterm formula when the mother's own milk is not available. Although the current trial data indicate that donor human milk reduces the risk



for NEC, it does not lower BPD risk or improve long-term neurodevelopmental outcomes. (118)

## CONCLUSION

BPD remains the most common chronic complication associated with extremely preterm birth. Strategies to minimize lung injury and prevent BPD must begin in the immediate perinatal period and likely continue throughout hospitalization. Initial respiratory care of very preterm infants should begin with nasal CPAP, with endotracheal intubation and surfactant administration reserved for those who fail noninvasive support or do not demonstrate spontaneous respiratory effort after resuscitation. For infants receiving invasive mechanical ventilation, use of a volume-targeted approach rather than pressure-limited ventilation may reduce BPD risk. Caffeine and vitamin A are the only medications with high-quality evidence to support routine use for BPD prevention. Dexamethasone is an effective therapy, but for many infants, the risks for adverse effects with this medication outweigh the benefits. However, for those at high risk of developing BPD, dexamethasone initiated after the first week of age may be appropriate. Hydrocortisone is an alternative option that has been shown in RCTs to reduce rates of death or BPD when initiated in the first week of age. Unfortunately, this benefit may come at the expense of higher rates of sepsis and gastrointestinal perforation without advantages for long-term neurodevelopment. Less invasive surfactant administration is a promising intervention currently under investigation.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Be aware of various preventive strategies for bronchopulmonary dysplasia/chronic lung disease.

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1. Bronchopulmonary dysplasia (BPD) is a common complication of prematurity and is associated with significant long-term morbidities including chronic respiratory and cardiovascular disorders, growth failure, and adverse neurodevelopmental outcomes. Ventilator-induced lung injury is an important factor contributing to the development of BPD and therefore the use of noninvasive respiratory support in very preterm infants has been extensively studied. Which of the following statements regarding the use of noninvasive positive airway pressure to prevent BPD is correct?
  - A. Meta-analyses indicate an increased risk of pneumothorax with the use of early continuous positive airway pressure (CPAP) as initial mode of support.
  - B. Meta-analyses indicate a small but significant reduction in the risk of death or BPD with early CPAP therapy.
  - C. Heated and humidified high-flow nasal cannula has been shown to be equivalent to nasal CPAP for postextubation support.
  - D. Nasal intermittent positive pressure ventilation (NIPPV) decreases BPD when used as the initial mode of respiratory support.
  - E. Synchronized NIPPV has not been shown to be superior to asynchronous NIPPV with regard to BPD prevention.
2. Although noninvasive respiratory support is the preferred approach for most preterm infants, surfactant administration should be considered in preterm infants requiring intubation and mechanical ventilation. Which of the following statements regarding surfactant administration is correct?
  - A. Surfactant administration after 1 hour of age does not reduce the risk for BPD.
  - B. Lucinactant, a synthetic surfactant containing a peptide analog of protein B, has a lower efficacy than animal-derived surfactants.
  - C. The INSURE (intubation, surfactant administration during brief mechanical ventilation, followed by extubation) technique has been shown to decrease the risk for BPD compared with CPAP alone.
  - D. Less invasive surfactant administration techniques reduce BPD risk among survivors compared with control therapies.
  - E. In a recent Bayesian network meta-analysis, nebulized surfactant administered via laryngeal mask airway was associated with the largest reduction in the risk for death or BPD.
3. BPD is multifactorial and strategies for prevention must include multiple evidence-based practices. Which of the following statements regarding pharmacologic measures to prevent BPD in preterm infants is FALSE?
  - A. Azithromycin reduces the risk for death or BPD in preterm infants colonized or infected with *Ureaplasma*.
  - B. Caffeine decreases the risk for BPD in preterm infants with birthweights of 500 to 1,250 g.
  - C. Intramuscular injections of vitamin A for 4 weeks after birth has been shown to decrease BPD in extremely low-birthweight infant survivors.
  - D. In the PREMIOLOC trial, hydrocortisone within the first 24 hours after birth was associated with an increased risk of late-onset sepsis in infants born at 24 to 25 weeks.
  - E. In the multicenter NEUROSIS trial, inhaled budesonide reduced the risk for BPD in survivors but was associated with increased mortality.

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4. Corticosteroids are attractive therapeutic agents for BPD prevention because of their potent anti-inflammatory properties. Among corticosteroid agents, dexamethasone has been the most studied. Which of the following statements regarding the use of dexamethasone to decrease BPD is correct?
- A. Early dexamethasone is defined as treatment initiation within 14 days of birth.
  - B. Early dexamethasone treatment is associated with increased risk of gastrointestinal perforation and hypertrophic cardiomyopathy, but not cerebral palsy.
  - C. In a meta-analysis of late dexamethasone use, the risk for cerebral palsy was found to be significantly increased in dexamethasone-treated infants.
  - D. Based on a meta-regression study by Doyle et al, late dexamethasone should be considered in infants in whom the risk for BPD exceeds 80%.
  - E. In the Dexamethasone: A Randomized Trial (DART) study, low-dose dexamethasone did not result in lower BPD risk.
5. In very preterm infants in the NICU, BPD has remained a challenging morbidity to prevent and treat. Which of the following interventions or practices in neonatal care has been associated with lower BPD risk either in controlled trials or consistently in observational studies?
- A. Donor human milk.
  - B. Inhaled nitric oxide in early preventive strategies, but only for non-black patients.
  - C. Higher fluid intake during the first week after birth.
  - D. Indomethacin prophylaxis or treatment for patent ductus arteriosus within the first week after birth.
  - E. Low-dose hydrocortisone initiated soon after birth for a 10-day course.



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# Neonatal Respiratory Support on Transport

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## Education Gaps

Evaluation for and use of respiratory support remains a common occurrence in neonatal interfacility transport. Clinicians should be aware of the available types of respiratory support and their appropriate uses, as well as how to respond to respiratory emergencies to decrease the risk of complications during transport and improve health outcomes.

## Abstract

Respiratory support is frequently required during neonatal transport. This review identifies the various modalities of respiratory support available during neonatal transport and their appropriate clinical uses. The respiratory equipment required during neonatal transport and appropriate safety checks are also reviewed. In addition, we discuss potential respiratory emergencies and how to respond to them to decrease the risk of complications during transport and improve health outcomes.

## Objectives After completing this article, readers should be able to:

1. Describe the different modalities of respiratory support available for neonatal transport and their appropriate clinical use.
2. Review respiratory equipment and safety checks before transporting a patient receiving respiratory support.
3. Describe the potential effects of transport on respiratory support.
4. Identify respiratory emergencies during transport and how to manage them.

## INTRODUCTION

The need for respiratory support remains a frequent occurrence for neonatal interfacility transport teams. The primary reason for transfer may be respiratory-based, such as premature infants with respiratory distress syndrome (RDS), infants with meconium aspiration syndrome (MAS), infants with persistent pulmonary hypertension (PPHN), or infants with airway obstruction. However, the need for respiratory support may also stem from other underlying

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### ABBREVIATIONS

CPAP	continuous positive airway pressure
ECMO	extracorporeal membrane oxygenation
ETT	endotracheal tube
Fio <sub>2</sub>	fraction of inspired oxygen
HFV	high-frequency ventilation
iNO	inhaled nitric oxide
IV	intravenous
LMA	laryngeal mask airway
MAS	meconium aspiration syndrome
NCPAP	nasal continuous positive airway pressure
PPHN	persistent pulmonary hypertension
RDS	respiratory distress syndrome
RT	respiratory therapist

diagnoses such as congenital diaphragmatic hernia, abdominal mass, genetic syndrome, congenital cardiac defect, or metabolic disorder. Several types of respiratory support can be used during neonatal transport; these options are summarized in Table 1. (1) Members of the transport team should have a comprehensive understanding of these possible interventions. This review details the different types of respiratory support, their indications for use, and how to address respiratory emergencies during transport.

CLINICAL CONSIDERATIONS: WHEN TO USE EACH MODALITY

After receiving a call for neonatal transport, it is vital to have a detailed discussion about the patient’s potential respiratory support requirements. The content of this discussion will frequently influence many steps in the transport process, most importantly, whether additional equipment is required and potentially the makeup of the transport team itself. The transport team should also account for possible changes in the patient’s status en route to the referring hospital. The patient’s gestational age, weight, and underlying condition will frequently guide the mode and degree of support required.

Respiratory Distress Syndrome

The incidence of RDS is inversely proportional to birth gestational age. Other risk factors for RDS include maternal diabetes and lack of antenatal steroids. Affected infants will

need positive pressure support, with either noninvasive ventilation or intubation and mechanical ventilation. In the past, many infants with RDS required automatic intubation for transport. However, with the improvement in use of antenatal steroids, availability of continuous positive airway pressure (CPAP) in the delivery room, the administration of intratracheal surfactant, and recent availability of noninvasive ventilation during transport, the use of noninvasive respiratory support for this patient population has increased.

After arrival at the outside hospital, the transport team will need to decide what level of support the patient will need. Should the patient be intubated? Should surfactant be given before transport? Surfactant therapy has had a profound impact on patients in the NICU by reducing oxygen and ventilation requirements. Many studies have investigated the impact of administering surfactant before transport and found it to be safe, with the caveat being that those administering surfactant should have the “technical and clinical expertise to administer surfactant safely.” (2) Therefore, pediatric clinicians who are without expertise, or who are inexperienced or uncomfortable with surfactant administration or managing an infant who has received surfactant should wait for the transport team to arrive. (3) In addition, the potential side effects of sudden hypoxemia, displacement or plugging of the endotracheal tube (ETT), development of an air leak because of a sudden change in compliance, development of a pulmonary hemorrhage, and hyperventilation should also be considered. (3) A retrospective review published in 2010 concluded that, in a

TABLE 1. Types of Respiratory Support During Neonatal Transport

Noninvasive respiratory support (1)	1. Oxygen hood or free-flowing oxygen delivered into the incubator 2. Low-flow nasal cannula delivering <2 L/min 3. Humidified, heated high-flow nasal cannula delivering ≥2 L/min 4. Continuous positive airway pressure 5. Noninvasive intermittent positive pressure ventilation
Invasive respiratory support	1. Conventional mechanical ventilation (CMV) with settings of: -Peak inspiratory pressure -Positive end-expiratory pressure -Rate -Inspiratory:expiratory ratio -Fraction of inspired oxygen <i>Indications for CMV: respiratory distress worsening with increasing oxygen requirement, recurrent apnea, cyanotic heart disease, congenital diaphragmatic hernia</i> 2. High-frequency ventilation: High-frequency flow interrupter most widely available; settings include: -Mean airway pressure -Amplitude -Hertz <i>Indications for HFV: reduce volutrauma, air leak syndrome, infants who fail CMV</i>

cohort of over 200 infants who received surfactant before transport, the rate of pneumothorax was only 2.9% compared with the incidence of hyperventilation, which was 18.9%. They also noted that infants who were hyperventilated also had longer transport times, lower birthweights, and lower  $P_{CO_2}$  levels before transfer to the tertiary center. (4)

The use of nasal CPAP (NCPAP) is known to reduce the need for intubation and the incidence of bronchopulmonary dysplasia in infants with RDS. A 2014 study by Jani et al found that the use of NCPAP in preterm infants (28–31 weeks' gestation) was both safe and effective when performed by a dedicated transport team. (5) Based on their retrospective study, the authors developed some practical recommendations for the use of NCPAP during transport:

- A blood gas measurement should be obtained either at the time of stabilization for transport or 30 minutes after starting NCPAP
- Administration of caffeine to very premature infants receiving NCPAP
- Intubation should be considered if the infant develops moderate to severe respiratory distress while receiving NCPAP ( $CPAP > 6$  cm  $H_2O$ ) with a fraction of inspired oxygen ( $F_{IO_2}$ )  $> 0.3$  and blood  $P_{CO_2} > 55$  mm Hg (7.3 kPa). Frequent episodes of apnea while receiving NCPAP are also an indication for intubation. (5)

The *intubation, surfactant, extubation* (INSURE) technique of intubation—administration of surfactant followed by extubation—has been found to preserve the benefits of surfactant treatment while avoiding the potential side effects of mechanical ventilation. The use of this technique in the setting of transport was analyzed in a retrospective study examining moderately preterm infants ( $> 28$  weeks' gestation) with RDS who underwent intubation and required transfer to a tertiary referral center. The authors examined whether there were clinical indicators associated with those infants who underwent extubation shortly after transport, and thus would potentially be candidates for INSURE and transport with NCPAP. Although infants who underwent early extubation had a significantly lower  $F_{IO_2}$  after surfactant administration and stabilization by the transport team, the authors concluded that  $F_{IO_2}$  only had a weak positive predictive value for extubation to NCPAP before transport. (6)

### Air Leak

Pulmonary air leak can occur in newborns with underlying pulmonary disease and those receiving positive pressure. (7) Thus, the clinical team should obtain a chest radiograph before transporting infants with respiratory distress.

Significant neonatal risk factors for a pulmonary air leak include MAS, preterm birth with RDS, and pulmonary hypoplasia. The use of a long inspiratory time, high peak pressures, and large tidal volumes are also considered risk factors. An air leak occurs as a result of overdistention of alveoli from uneven air distribution leading to alveolar rupture. (8) Air can dissect into the perivascular connective tissue presenting in different forms: pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, and pneumopericardium. (9)

Frequently, an infant with a pneumothorax may initially appear to be asymptomatic and only later present with a rapid clinical deterioration. An increase in  $F_{IO_2}$  requirement, asymmetric breath sounds, chest asymmetry, and shifting of the apex beat may be clinical indicators of a pneumothorax. Transillumination of the chest may be helpful to diagnose a pneumothorax, with confirmation obtained on radiography, if available.

Treatment of a pneumothorax before transport will depend on the size of the air leak. A small pneumothorax in a clinically stable infant may be managed with mild respiratory support, such as a nasal cannula. Nitrogen washout with the use of oxygen supplementation with an  $F_{IO_2}$  of 1.0 has not been shown to hasten resolution of the pneumothorax. (10) A large pneumothorax will likely need a definitive chest tube placed before transport. A moderate pneumothorax may potentially be treated definitively with needle thoracentesis; however, chest tube placement should be considered before transport.

There are special considerations for transporting a newborn with a pneumothorax by air. Transport personnel should consider the potential impact of altitude on air leak and air collections. The Boyle law states that entrapped gas expands by 3% for every increase in altitude of 1,000 ft. Thus, a small pneumothorax may increase with increasing altitude.

For infants with an air leak of any type who are receiving mechanical ventilation, minimizing the mean airway pressure will help offset the accumulation or reaccumulation of air. High-frequency ventilation (HFV) has been found to provide adequate gas exchange using very low tidal volumes and a supraphysiologic rate, and thus HFV may be a useful option if there is concern for ongoing air leak. Although evidence that HFV prevents air leaks from occurring is insufficient, its use in the management of air leaks is ubiquitous and has not been found to be harmful. (11)

### Persistent Pulmonary Hypertension

A number of disease processes can lead to pulmonary hypertension in the neonatal period. These include acute

hypoxia because of perinatal depression, RDS, pneumonia, MAS, severe intrauterine growth restriction, and pulmonary hypoplasia. (12) High pulmonary vascular resistance favors blood flow to the systemic circulation leading to a differential cyanosis of more than 5% to 10% between the lower limb and the right upper limb. (13) This disease process is managed by optimizing ventilatory support, either with the conventional ventilator or with HFV, surfactant administration, inhaled nitric oxide (iNO), and if needed, extracorporeal membrane oxygenation (ECMO). When these treatments are not available to an infant with a presumed diagnosis of PPHN, the infant must be transferred to a tertiary referral center by an experienced transport team that is equipped with iNO. (14)

Nitric oxide is a potent inhaled pulmonary vasodilator that has been shown to reduce the need for ECMO in newborns with PPHN. (15) Lowe and Trautwein examined the benefits of starting iNO in the outlying hospital before transport to a tertiary center. They found that the initiation of iNO before transport did not alter infant mortality rate or need for ECMO. (16) However, in patients who did not need ECMO, early administration of iNO significantly reduced the receiving hospital length of stay, in addition to the total (combined referring and receiving hospital) length of stay. (16)

Up to 40% of infants with diseases such as parenchymal disease, pulmonary vascular disease, and cardiac dysfunction will not respond to iNO for a wide variety of reasons such as parenchymal disease, pulmonary vascular disease, and cardiac dysfunction. (17) Optimizing lung expansion by using HFV in addition to improving cardiac function with inotropic support may be necessary considerations. (17) A retrospective study by Mainali et al found that high-frequency jet ventilation during transport was shown to significantly improve ventilation in neonates before receiving ECMO. (18)

Labile hypoxemia can be a characteristic of PPHN as a result of the delicate balance between pulmonary vascular resistance and systemic vascular resistance. (13) The transport team should monitor pre- and postductal oxygen saturations during transport in infants at risk for PPHN.

## RESPIRATORY SIDE EFFECTS OF TRANSPORT

Respiratory side effects of transporting a newborn can vary. Before being transported, it is paramount that the infant achieves respiratory stability, because transfer of an unstable infant can potentially worsen the infant's clinical condition. During transport, patients can develop hypoxemia and hypercapnia but may also develop hyperoxia and hypocapnia.

(19) Many physiologic stressors are associated with transport, particularly aeromedical transport, which is affected by the Boyle law (the expansion of gas with rising altitude), Dalton law (the partial pressure of gas decreases with increasing altitude), and Henry law (the solubility of gas alters with a changing altitude). (20) All of these issues may be negated somewhat by the presence of cabin pressurization in a fixed wing aircraft. In contrast, helicopters are not pressurized and therefore limited to less than 10,000 ft, with typical flying altitudes of 1,000 to 3,000 ft. Lung volume can expand at altitudes as low as 1,000 ft, with volume expansion of up to 13.8% occurring in an artificial pneumothorax model at 5,000 ft. (21) During transport, it is important to be cognizant of these potential physiologic stressors and anticipate potential complications.

### Hypoxemia

Lollgen et al examined oxygen saturation levels during aeromedical transport of infants younger than 6 months and found that desaturations (<94%) occurred in about a third of infants, with a trend toward an increased incidence in younger infants (44.4% at 6 weeks of age vs 18% at 3 months of age vs 16% at 3–6 months of age). (22) Factors such as ventilation/perfusion mismatch, increased fetal hemoglobin, pulmonary vasoconstriction, and smaller airway diameter are believed to contribute to altitude-associated hypoxemia in infants. (23)(24)(25) The British Thoracic Society 2004 guidelines for commercial air travel recommend that infants with oxygen saturation less than 90% receive supplemental oxygen during transport. (26)

### Gas Expansion

Gas expansion may occur in a number of areas in a neonate, most notably in the gastrointestinal tract. During transport, this side effect can be proactively managed by placement of a nasogastric or orogastric tube in infants receiving mechanical ventilation and those at risk for vomiting. Extra caution should be taken when transporting an infant with a pneumothorax because frequent reevaluation is necessary and the transport team should be prepared for a possible needle thoracentesis if the air leak worsens. If more air accumulates and the transport occurs via air travel, the transport team could potentially request that the pilot fly at a lower altitude to minimize additional air leaks.

### Vibration

Vibration is inherent in all types of transport. Vibration can be a significant physiologic stressor, particularly during helicopter transports. This stress may worsen respiratory distress. In a study of rat pups, the authors found that the



forces transmitted to the animals during a simulated medical transport caused a significant deterioration in their pulmonary function with increasing duration of the transport. Most notably, there was a significant increase in airway resistance at a given positive end-expiratory pressure. (27)

### Thermoregulation

Temperature variation may occur with both air and ground transport. Alteration in the environmental temperature may be caused by seasonal changes, geographic factors, or alteration in altitude (20). Changes in the external temperature may alter the infant's metabolic rate, respiratory status, and oxygen demand, potentially further compromising a hypoxemic infant. To ameliorate these variations as much as possible, the transport team should take steps such as using a warming mattress, using additional clothing, and removing any wet clothing or dressings in a timely manner.

## PROFESSIONAL RESPIRATORY SUPPORT

Neonatal transport teams are made up of a varying combination of nurses, physicians, and paramedical staff. (14) A survey of 335 neonatal transport teams in the United States found 26 different team compositions, (28) with the most common being nurse–respiratory therapist (RT)–based teams. However, not every facility has the capability of

having an RT participate in transports. If an RT is not available, the transport team should be aware of the RT-related responsibilities during transport, (20) which include the following:

- Check the oxygen and air levels in the cylinders on the transport bed
- Ensure that the ventilator circuit is attached and operational and know how to use different modes of respiratory support on transport
- Ensure that the transport bag is fully stocked and secured
- Bring the appropriate surfactant dose in a cooling pack and be experienced in surfactant administration
- Bring a portable blood gas machine (if available) and be experienced with its use
- Check the transport ambulance to ensure that the electrical inverter is working properly
- Check the transport ambulance to ensure that an adequate oxygen supply is available
- Complete transport evaluation form (may be composed of various metrics such as departure time, arrival time, time spent at referring facility, patient temperature at the time of admission to receiving facility).

Although the transport team composition can vary greatly, the team's training seems to be the most important factor affecting patient outcomes. The use of specialized transport teams to transfer critically ill pediatric patients was

TABLE 2. Respiratory Care Transport Equipment (47)

Airway equipment	<p>Neonatal positive pressure bags with neonatal and infant mask, positive end-expiratory pressure valve, manometer</p> <p>Continuous positive pressure airway apparatus; nasal prongs, assorted sizes</p> <p>Nasal cannula, premature and newborn sizes</p> <p>Endotracheal tubes (ETTs): 2.5, 3.0, 3.5, 4.0 mm, stylets, (ETT holders/tape to secure ETT)</p> <p>Laryngoscope with size 00, 0, and 1 blades (extra batteries and extra light)</p> <p>Capnography/carbon dioxide detector or monitor</p> <p>Mechanical ventilator with back up circuit</p> <p>Oxygen and air cylinders with appropriate indicators of in-line pressure and gas content</p> <p>Flow meters, oxygen tubing and adapters</p> <p>Oxygen analyzer, pulse oximeter and probes</p> <p>Laryngeal mask airway—preterm and term (size 0.5 and 1)</p> <p>Surfactant administration devices</p> <p>Inhaled nitric oxide and delivery system</p> <p>Chest tubes—8F, 10F, 12F</p>
Suction equipment	<p>Bulb syringe</p> <p>Suction catheters—5F, 6F, 8F, 10F, 12F</p> <p>Regulated suction with gauging limiting</p> <p>Orogastric/nasogastric feeding tube 8F and 10F and 20-mL syringe for orogastric decompression</p> <p>Mucous suction trap, sterile gloves and sterile water for irrigation</p>
Monitoring equipment	<p>Stethoscope, electrocardiography leads, cardiac monitor, pulse oximeter</p> <p>Glucometer for blood sugar evaluation, blood gas evaluation</p> <p>Capnography (transcutaneous or in-line)</p>

found to improve survival rates and to reduce the number of unplanned events during transport of critically ill pediatric patients. (29)

## PRETRANSPORT INFANT STABILIZATION

It is essential to stabilize a sick neonate before transport to help maintain normothermia, adequate oxygenation and perfusion, and euglycemia throughout the transport. (30) The acronym “TOPS” (temperature, oxygenation [airway and breathing], perfusion, and sugar) can serve as a quick reminder of stabilization requirements before transferring an infant to a tertiary center. (30)

1. Arrival responsibilities: Assess infant’s temperature, airway, breathing, circulation, and blood sugar.
2. Temperature: Correct hypothermia (eg, warm clothing, portable heating mattress) if present before transport.
3. Oxygenation
  - a. Airway: Assess airway for presence of secretions and suction, if needed; assess need for shoulder/neck roll; secure ETT if intubated.
  - b. Breathing: Assess for respiratory distress; assess whether infant requires respiratory support and/or ventilation; assess recent blood gas and chest radiograph; verify ETT placement and chest tube function, if applicable; adjust vent support, as indicated; determine if surfactant is indicated (if so, prepare for change in compliance after administration; if  $\text{Fio}_2$  decreases after administration, assess breath sounds because pressure might need to be decreased as well).
4. Perfusion/circulation: Assess heart rate, blood pressure, and urine output; verify and check all intravenous (IV) fluid infusions and any medication infusions; adjust fluids and medications as indicated; verify that all lines are secured for transport.
5. Sugar: Check blood glucose level; if glucose  $<40$  mg/dL (2.2 mmol/L), give an IV bolus of 2 mL/kg of 10% dextrose in water, and then assess patency of the IV tube, increase maintenance glucose infusion, and obtain another blood glucose level to determine response and next steps.
6. Transport personnel: Receive report from referring hospital; update parents; obtain consent for transport; provide parents with contact information at tertiary center.
7. Equipment: Verify all equipment needed and its correct functioning. This should occur before going to the referral hospital and before leaving the referring hospital with the patient (Table 2).

## SPECIAL CONSIDERATIONS

Interfacility neonatal transport occurs frequently for primary respiratory issues but special consideration should be given to clinical situations in which the respiratory system is not the main reason for transport. However, the transport team should anticipate the possibility of respiratory complications as potential sequelae of other underlying diagnoses.

### Use of Prostaglandin

Evaluation for a suspected congenital heart disease remains a common reason for neonatal transfer to a tertiary care center. A continuous prostaglandin  $\text{E}_1$  infusion is vital in maintaining the patency of the ductus arteriosus in ductal-dependent cardiac lesions. Common side effects of prostaglandin  $\text{E}_1$  are hypoventilation and apnea, affecting 7.7% to 20% of infants. (31)(32)(33) Establishment of a secure airway before initiating prostaglandin  $\text{E}_1$  therapy and interfacility transport should be considered to decrease the risk of transport complications.

### Concern for Seizure Activity

The highest incidence of seizures in the pediatric population is seen during the neonatal period. The need for subspecialty support for antiseizure medications and management of the underlying causes often requires transport to a tertiary care center. Symptoms of seizure activity include involuntary movements of the extremities, apnea, and autonomic function alterations in the heart rate, blood pressure, or oxygenation. In addition, most antiepileptic drugs have sedative effects that can be significant enough to depress respiratory drive. (34)(35)(36) The need for respiratory support during transport should be anticipated before leaving the referring hospital and should take into account the infant’s seizure symptoms and severity as well as the dose of antiepileptic drugs.

### Use of Analgesics and Sedatives

Opioids and benzodiazepines are often administered as analgesics and/or sedatives to treat an underlying problem or to stabilize a neonate before transport. The desired clinical effects must be balanced with both the consequential clinical effects and the side effects of these medications. Infants are at risk for oversedation and/or respiratory depression when receiving these medications. (35)(37) The need for respiratory support to offset these effects should be anticipated during evaluation and stabilization before transport to the tertiary center.

## ACUTE RESPIRATORY DECOMPENSATION

Although interfacility transport has been demonstrated to improve overall outcomes and care of critically ill neonates, transport is not without risk. An acute decompensation in an infant's clinical status may be encountered by transport teams despite stabilizing a patient before transport. The underlying cause of an acute respiratory decompensation should be recognized and addressed as quickly as possible to minimize mortality and morbidity during transport. The most common respiratory issues that can occur are:

1. Accidental extubation
  - a. Signs and symptoms: Decreased oxygen saturation, bradycardia, and increased work of breathing unresponsive to increased respiratory support and suctioning; absent or diminished breath sounds bilaterally; absent color change seen on carbon dioxide detector.
  - b. Management
    - i. Removal of ETT and initiation of bag-mask ventilation.
    - ii. Suctioning of secretions.
    - iii. Reintubation if possible during transit. If not possible, continue bag-mask ventilation until the ambulance or flight can be stopped to facilitate reintubation.
    - iv. Alternatively, a laryngeal mask airway (LMA) may be placed. According to the International Liaison Committee on Resuscitation and European Resuscitation Council guidelines, LMAs may be used in late preterm infants and term infants weighing more than 2,000 g. (38)(39) However, LMAs have been successfully placed in low-birthweight infants (1,000–1,500 g) during delivery room resuscitation and in preterm infants (>29 3/7 weeks' gestation). (40)(41) The role of LMA in neonatal transport has been described in multiple case reports, but no randomized controlled trials have compared its effectiveness with other means of respiratory support. (42)(43).
2. Pneumothorax
  - a. Signs and symptoms: Decreased oxygen saturation, bradycardia, and hypotension, and increased work of breathing unresponsive to increased respiratory support and suctioning; asymmetric breath sounds or chest expansion; translucency of chest cavity on transillumination of affected side.
  - b. Management
    - i. In cases of tension pneumothorax, perform needle decompression using a butterfly needle or an

angiocatheter in the second intercostal space in the midclavicular line or fourth intercostal space anterior to the midaxillary line.

- ii. When no more air can be withdrawn, remove the needle.
  - iii. If there is an ongoing leak, the team can consider keeping an angiocatheter in place with the distal end of tubing placed under sterile water to create a seal (44) or attached to a Heimlich valve via tubing; however, experience with this technique is necessary before applying it during transport.
  - iv. Placement of a chest tube may be required.
3. Pulmonary hemorrhage
    - a. Signs and symptoms: Fresh blood or blood-tinged secretions in the ETT; increased work of breathing, increased ventilatory requirements.
    - b. Management
      - i. Suctioning.
      - ii. Increase positive end expiratory pressure.
      - iii. Consider blood component therapy, if available.
      - iv. Consider administration of 1:10,000 epinephrine via ETT. Dosing varies in different studies from 0.1 mL/kg to 0.5 mL. (45) (46)

## SUMMARY

- Various types of respiratory modalities are available for use during transport of a critically ill infant.
- A thorough clinical assessment of the patient, taking additional comorbidities into account, will help guide the patient's respiratory needs for transport.
- It is important to be prepared for a possible clinical deterioration in the patient by bringing the appropriate equipment and having adequate and appropriate staffing.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the issues in the organization of perinatal care (eg, regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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1. A male infant is born at 32 weeks' gestational age at a hospital without the capacity to support infants receiving mechanical ventilation for longer than several hours. The infant initially has spontaneous breathing but progresses to have increasing respiratory distress over the first hour after delivery. The infant is requiring continuous positive airway pressure (CPAP) and increasing fraction of inspired oxygen ( $\text{FiO}_2$ ) support. A transport team from a higher level NICU is mobilized to accept the patient. As the decision to intubate and provide surfactant is being made, which of the following factors is an appropriate consideration?
  - A. If the infant was exposed to antenatal steroids, surfactant is contraindicated.
  - B. Because avoidance of intubation is a high priority, surfactant in this scenario is best administered with the use of nebulization through heated humidified nasal cannula.
  - C. Studies have consistently shown that surfactant administered just before transport is associated with a 25% incidence of pneumothorax.
  - D. Nasal CPAP often paradoxically increases the risk of intubation in early respiratory distress syndrome.
  - E. The health care professionals administering surfactant should have the technical and clinical expertise to administer surfactant safely, and in particular, should pay close attention to the potential complication of hyperventilation.
2. An infant born at 29 weeks' gestational age has respiratory distress syndrome and is receiving nasal CPAP. Arrangements are being made for the infant to be transported to a higher level of care. Which of the following statements about this clinical scenario is correct?
  - A. Because of the infant's gestational age, CPAP is not a safe mode of support during transport.
  - B. Lower  $\text{FiO}_2$  requirement during CPAP before surfactant administration is a highly predictive factor in the potential for successful extubation after the intubation, surfactant, extubation (INSURE) procedure.
  - C. Once the decision to apply CPAP has been made and appears to be working, the infant should continue to receive CPAP and not be intubated during transport, and the positive end-expiratory pressure increased as needed up to 10 cm  $\text{H}_2\text{O}$ .
  - D. Blood gas measurement for infants receiving CPAP would be advised either at stabilization or 30 minutes after starting CPAP.
  - E. Because of the potential for tachycardia, infants receiving CPAP during transport should not receive caffeine until they have been stabilized in the receiving hospital.
3. An infant born at 32 weeks' gestational age at a hospital without a NICU is being prepared for transport. In the delivery room, the infant receives CPAP via mask for several minutes for apnea which subsequently resolved. The infant has mild respiratory distress and is receiving nasal cannula oxygen. The chest radiograph shows a small pneumothorax on the right side. Which of the following concerning air leak in this population is correct?
  - A. Long inspiratory time, high peak pressures, and large tidal volumes are risk factors for pulmonary air leak.
  - B. Nitrogen washout is an effective treatment that should be implemented before transport for all patients with pneumothorax who require support.
  - C. Air transport may be a preferred mode because of the likelihood that air leak will reduce with higher altitudes.
  - D. Although a chest tube may ultimately be beneficial, placement should be postponed until admission to the NICU, as transport will likely lead to unplanned removal because of movement.
  - E. Higher mean airway pressure will facilitate air leak evacuation by pushing the air into interstitial spaces.

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4. An infant born at 40 weeks' gestational age is diagnosed with meconium aspiration syndrome and persistent pulmonary hypertension. Because of the need for higher level of care, arrangements are made for transport. Inhaled nitric oxide is initiated after increasing pressures and  $\text{Fio}_2$  during mechanical ventilation. Which of the following is most likely to be reduced because of the addition of inhaled nitric oxide treatment?
- A. Mortality.
  - B. Need for extracorporeal membrane oxygenation.
  - C. Hospital length of stay.
  - D. Hospital-acquired infection.
  - E. Anemia.
5. An infant born at 39 weeks' gestational age is noted to have mild respiratory distress and evaluation leads to a diagnosis of hypoplastic left heart syndrome. The infant is receiving nasal cannula oxygen and a peripheral intravenous line is placed. Prostaglandin is started to maintain patency of the ductus arteriosus. Arrangements for transport to a cardiac center are made. Which of the following is an important consideration for transport of this infant receiving prostaglandin?
- A. Low pressures for respiratory support and avoidance of intubation are suggested because of the high risk of pneumothorax in this population.
  - B. Inhaled nitric oxide is an important consideration for supplementing current therapy to improve pulmonary vascular dilation.
  - C. The most frequent side effect of prostaglandin in newborns is seizures.
  - D. Because hypoventilation and apnea are common side effects, establishment of a secure airway before initiating prostaglandin therapy and transport should be considered to decrease the risk of transport complications.
  - E. Optimal perfusion will be achieved by using high  $\text{Fio}_2$ .

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# Approaches to Noninvasive Respiratory Support in Preterm Infants: From CPAP to NAVA

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## Education Gaps

Invasive mechanical ventilation through an endotracheal tube has been the mainstay of treatment of respiratory distress syndrome in the preterm newborn. Efforts to decrease invasive ventilation have resulted in the development of multiple forms of noninvasive respiratory support. Clinicians should be familiar with these newer modes of noninvasive respiratory support and their long-term effects, if any, on pulmonary morbidities.

## Abstract

Endotracheal intubation and invasive mechanical ventilation have been mainstays in respiratory care of neonates with respiratory distress syndrome. Together with antenatal steroids and surfactant, this approach has accounted for significant reductions in neonatal mortality. However, with the increased survival of very low birthweight infants, the incidence of bronchopulmonary dysplasia (BPD), the primary respiratory morbidity of prematurity, has also increased. Arrest of alveolar growth and development and the abnormal development of the pulmonary vasculature after birth are the primary causes of BPD. However, invasive ventilation-associated lung inflammation and airway injury have long been believed to be important contributors. In fact, discontinuing invasive ventilation in favor of noninvasive respiratory support has been considered the single best approach that neonatologists can implement to reduce BPD. In this review, we present and discuss the mechanisms, efficacy, and long-term outcomes of the four main approaches to noninvasive respiratory support of the preterm infant currently in use: nasal continuous positive airway pressure, high-flow nasal cannula, nasal intermittent mandatory ventilation, and neurally adjusted ventilatory assist. We show that noninvasive ventilation can decrease rates of intubation and the need for invasive ventilation in preterm infants with respiratory distress syndrome. However, none of these noninvasive approaches decrease rates of BPD. Accordingly, noninvasive respiratory support should be considered for clinical goals other than the reduction of BPD.

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### ABBREVIATIONS

BPD	bronchopulmonary dysplasia
CPAP	continuous positive airway pressure
F <sub>IO<sub>2</sub></sub>	fraction of inspired oxygen
FRC	functional residual capacity
GA	gestational age
HFNC	high-flow nasal cannula
NAVA	neurally adjusted ventilatory assist
NCPAP	nasal continuous positive airway pressure
NIMV	nasal intermittent mandatory ventilation
NIV	noninvasive ventilation
PEEP	peak end-expiratory pressure
PIP	peak inspiratory pressure
RDS	respiratory distress syndrome

## Objectives After completing this article, readers should be able to:

1. Understand the principles, application, and indications for noninvasive respiratory support in the preterm newborn, including nasal continuous positive airway pressure, high-flow nasal cannula, nasal intermittent mandatory ventilation, and neurally adjusted ventilatory assist.

## INTRODUCTION

Mechanical ventilation through an endotracheal tube (invasive ventilation) has been the mainstay of treatment for preterm neonates with respiratory distress syndrome (RDS). Use of invasive mechanical ventilation, antenatal corticosteroids and postnatal surfactant has accounted for the reduction in neonatal mortality over the past 50 years. (1) However, invasive ventilation has been associated with the development of bronchopulmonary dysplasia (BPD), the primary pulmonary morbidity among survivors of RDS. Importantly, BPD is independently associated with increased risks of adverse neurodevelopmental outcomes. (2) While studies have used different criteria to define BPD, the most clinically important definition of BPD in infants <32 weeks of gestation is the requirement of at least 30% oxygen and/or positive pressure at 36 weeks' postmenstrual age. This definition corresponds to moderate/severe BPD, as defined by the National Institutes of Health severity-based diagnostic criteria. (3) Although arrest of alveolar growth and development is believed to be the primary cause of respiratory morbidity in preterm infants, (4)(5) invasive ventilation-associated lung inflammation and airway injury (6) have long been held to be important contributors. Proposed causes of invasive ventilation-associated injury include delivery of tidal volumes with positive pressure and oxygen toxicity. (7)

Because invasive ventilation has been associated with adverse effects on lung development, noninvasive approaches have been increasingly used. In this article, we present current approaches to noninvasive respiratory support, discussing the mechanism of each and its effects on BPD risk, and providing clinical recommendations for their uses.

## NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE

The development of endotracheal continuous positive airway pressure (CPAP) by Gregory in the early 1970s, as

described by Mai et al, revolutionized the treatment of infants with respiratory failure, and significantly improved mortality when compared with tidal ventilation alone. (8) Similar distending pressures can be delivered through the nares by means of large-bore nasal prongs without significant flow restriction. These nasal CPAP (NCPAP) devices deliver airflow that is continuously regulated to produce a set pressure, usually 4 to 7 cm H<sub>2</sub>O. NCPAP provides distending pressure to the airways and alveoli throughout the respiratory cycle. (9) By distending the lung, NCPAP increases functional residual capacity (FRC), which, in the preterm lung with reduced FRC, increases lung compliance. This increase, and the concomitant decrease in resistance at the distended upper airway, reduces the work of breathing. NCPAP also improves ventilation/perfusion matching, thereby improving oxygenation. Finally, by maintaining lung volume, NCPAP can prevent or reduce atelectasis. (10) As with all positive pressure delivery, NCPAP increases the risk of air leak syndromes, particularly pneumothorax, and is associated with gastric distention. (11) However, a recent randomized clinical trial of 44 preterm infants born at less than 30 weeks' gestation found no difference in time to full feedings with NCPAP compared with high-flow nasal cannula (HFNC). (12)

NCPAP, delivered through large-bore nasal prongs that do not restrict airflow, has been a mainstay of neonatal respiratory support. However, concerns about the comfort of infants during NCPAP treatment and the potential for trauma inside the nares due to pressure from the large-bore cannulas (13) have driven the development of alternate interfaces through which NCPAP is delivered. For example, a commercial nasal cannula (RAM cannula, Neotech, Valencia, CA) featuring small-bore, curved, plastic nasal prongs, has been widely adopted. However, the delivery of pressure through small RAM cannulas depends critically on the amount of leakage at the interface at the nares. Iyer

and Chatburn determined the impact of RAM cannulas on the delivery of peak end-expiratory pressure (PEEP) using a simulated neonatal nose and lung. (14) Neonatal RAM cannulas of 3 sizes were used, with prong external diameters of 3.0, 3.5, and 4.0 mm. The system was first designed to maintain a leak of 30% around the prongs. However, a larger (58%) leak was also created, labeled “worst case,” to mimic real-world situations. The outcome measured was the difference in pressures measured by the lung simulator compared with the set PEEP. For a nasal leak of 30%, 70% to 90% of set PEEP (at 5, 6, or 7 cm H<sub>2</sub>O) was transmitted across the nasal interface. However, with the “worst case,” as would occur with a size mismatch between nares and prong diameter, only 8% of PEEP was transmitted. Similar results were seen with tidal pressures delivered through the prongs (peak airway pressures set at 15, 20, and 25 cm H<sub>2</sub>O, similar to nasal intermittent mandatory ventilation [NIMV], as described later in this article) with peak airway pressures much higher with the smaller leak. Increased leakage of NCPAP prongs at the nose results in decreased transmission of desired distending pressure to the upper airway. (14) Because measurement of intrathoracic pressures developed by application of NCPAP is not clinically available, it is critical for practitioners and respiratory therapists to ensure that prongs are appropriately sized for the patient. The improved comfort of the infant receiving NCPAP through small-bore prongs is likely achieved at the cost of insufficient delivery of the clinically indicated pressure.

Finally, it is incumbent on practitioners and respiratory therapists to understand the extent to which the internal diameter of NCPAP prongs of each interface used provides the primary resistance to flow in the CPAP circuit. The contribution made by the inner diameter of the prongs to the measured pressure can be determined by setting the system to deliver a given pressure on a patient, and then removing the prongs from the patient’s nose. The pressure measured when the flow is delivered into the room indicates

the intrinsic resistance supplied by the prongs themselves, and therefore, the amount of distending pressure that the patient is not receiving.

Use of NCPAP improves survival and decreases the need for invasive ventilation compared with supplemental oxygen alone. Thus, in a recent, multicenter randomized, controlled trial, neonates born between 24 and 27 weeks’ gestation who received early NCPAP in the delivery room had increased survival and a decreased need for invasive ventilation at 7 days of age, compared with neonates who underwent intubation and were given surfactant within 1 hour after birth. (15) Notably, however, 4 large randomized, controlled trials evaluating routine CPAP versus routine intubation together found that 33% to 51% of high-risk infants initially treated with CPAP ultimately required intubation in the first week of postnatal age (Table 1). (15)(16)(17)(18)(19) Furthermore, approximately 25% of neonates required reintubation following surfactant plus a trial of NCPAP. (20) Thus, practitioners wishing to avoid intubation in very small infants may be best served by administering surfactant using a noninvasive approach (eg, the INTubation-SURfactant-Extubation [INSURE] method). (21) Although some randomized, controlled trials found that NCPAP reduces the rate of BPD, the treatment effect is small and has not been consistently reported in other trials. (22)

## HIGH-FLOW NASAL CANNULA

HFNC provides a heated and humidified oxygen mixture delivered via prongs in the nares at a controlled flow rate. In this modality, the pressure that the nasal airflow produces in the airway and chest is not monitored. The prongs typically used to deliver HFNC support have been associated with lower occurrences of nasal trauma compared with the large-bore prongs used to deliver NCPAP. It is a common perception among bedside nurses that these smaller and softer nasal prongs are better tolerated by premature

TABLE 1. Incidence of CPAP Failure

TRIAL	YEAR	SUBJECTS ENROLLED, NO.	GA (WK)	ACS, % (ANY)	CPAP FAILURE, % (5-7 DAYS)
COIN (17)	2008	610	25 0/7–28 6/7	94	46
SUPPORT (15)	2010	1316	24 0/7–27 6/7	>95	51.2
CURPAP (18)	2010	208	25 0/7–28 6/7	>95	33
Dunn (19)	2011	648	26 0/7–29 6/7	>98	45.1

These large randomized controlled trials evaluated CPAP alone as a primary mode of respiratory support. ACS=antenatal corticosteroids; CPAP=continuous positive airway pressure; GA=gestational age. Reprinted with permission from Wright et al. (16)



neonates. (23) Parents also prefer HFNC for their neonates, as they are able to better interact with their child and take part in their child's care. (24) Similar to NCPAP, HFNC may improve the work of breathing by reducing resistance in the upper airway and may improve ventilation by providing distending pressure for lung recruitment. (25)

HFNC has become increasingly popular in NICUs. HFNC has been used as primary respiratory support for premature infants. (26) However, evidence is increasing that **it is inferior to NCPAP** when used as primary therapy—many patients treated with HFNC subsequently require NCPAP or mechanical ventilation. (23) Thus, Conte and colleagues performed a meta-analysis of 6 randomized controlled studies comparing HFNC and NCPAP as initial support for RDS. This analysis, encompassing more than 1,200 infants who were born after 27 weeks' gestation, demonstrated that the initial use of HFNC resulted in a **higher rate of intubation** (treatment failure) compared with the initial use of NCPAP. (27) Similarly, a study of infants with more than or equal to 28 weeks of gestation supported with HFNC found almost **double the rate of treatment failure** (25.5%) compared with those receiving NCPAP (13.3%). (28) One reason for these consistent results may be the failure of HFNC to deliver appropriate distending pressures to the preterm lung.

As discussed before, distending pressure is the key to improving function of the preterm lung. With HFNC, the distending pressure resulting from delivered flow varies as a function of the flow and the resistance to flow presented by the inner diameter of the nasal cannula. Locke et al measured transthoracic pressures with an esophageal balloon in preterm infants receiving HFNC at different flow rates using cannulas of varying diameters. (29) Using 0.2-cm-diameter cannulas, distending pressure was not delivered, regardless of the amount of flow that was studied. In contrast, a 50% increase in cannula diameter (which decreases resistance as the fourth power of the radius) resulted in potentially dangerous (and clinically unmonitored) pressures of almost 10 cm H<sub>2</sub>O. **It is not unreasonable to conclude that the distending pressures developed by HFNC at commonly used, higher flow rates (4–5 L/min) may result in complications from overly high airway pressures.**

These data indicate that, in the clinical setting, the relationship between the airway pressure developed at a given flow rate in an individual patient receiving HFNC is unknown. As a result, infants may receive either insufficient distending pressure to improve pulmonary function or, worse, too much pressure resulting in lung overdistention, potentially increased work of breathing, and decreased

venous return. (30) These limitations make HFNC a less-than-ideal treatment for premature neonates whose primary respiratory requirement, at any time in the RDS course, is distending pressure. **In fact, an argument could be made for never using HFNC as an alternative to NCPAP, because the delivered pressure is unmonitored.** However, infants in whom prolonged NCPAP has led to nasal trauma may be candidates for the brief use of HFNC **at low flow rates.**

## NONINVASIVE VENTILATION

For many preterm infants with RDS, NCPAP may provide insufficient respiratory support. The concern that invasive ventilation increases BPD risk has led to extensive research into noninvasive forms of ventilation in neonates. (31) In noninvasive ventilation (NIV), pressure-regulated volumes are delivered periodically by a mechanical ventilator to a spontaneously breathing infant through a circuit interfaced to the nose with nasal prongs. NIV supports the infant's spontaneous breathing by periodically increasing intrathoracic pressure above CPAP for a set duration (analogous to inspiratory time in invasive ventilation). (32) Peak pressures and inspiratory times are set on the ventilator, but the extent to which the peak pressure is transmitted from the upper airway to the lung is unclear. Any resultant tidal volumes received by the infant occur as a function of the set peak pressure and the infant's overall respiratory mechanics.

In adults and older children, NIV, delivered by oronasal masks, has been more successful in preventing subsequent intubation than CPAP alone. (32) This increased mean airway pressure aids in maintaining end-expiratory lung volume, increasing FRC, and improving oxygenation. NIV has shown similar success in newborns, preventing intubation in some neonates who would otherwise fail NCPAP. (32) In addition, NIV has been shown to reduce the magnitude and severity of apnea. (33) Commonly used approaches to NIV have been **NIMV** and neurally adjusted ventilatory assist (**NAVA**).

## NASAL INTERMITTENT MANDATORY VENTILATION

NIMV is the most commonly used form of NIV in neonates. (32) With NIMV, neonates breathe spontaneously over NCPAP. Mandatory pressure control breaths are used, as described before, and are triggered by patient inspiration or delivered regularly without regard for the infant's respiratory cycle. (34)

One important question when evaluating NIMV is its efficacy in addressing pulmonary function particular to the preterm infant compared with NCPAP, specifically

oxygenation, ventilation, and respiratory drive. In an early study, Friedlich et al randomized 41 preterm infants with RDS (mean gestational age [GA] 27.8 weeks, mean birthweight 954 g) to receive NIMV or NCPAP following extubation and a mean duration of invasive ventilation of 23 days. (35) Infants receiving NIMV were significantly less likely to have respiratory failure using strict criteria. Biscaglia et al randomized 88 preterm neonates with mild to moderate RDS (fraction of inspired oxygen  $[F_iO_2] < 0.4$ , and a chest radiograph suggestive of RDS) to NIMV or NCPAP after birth. Although there was no difference in mean  $Pao_2$  values between the groups, infants receiving NIMV had lower mean  $Pco_2$  levels, fewer episodes of apnea, and a shorter duration of respiratory support compared with infants receiving NCPAP. (36) Accordingly, **the results of this single study support the use of NIMV over NCPAP in infants with mild to moderate disease.** In a study of sicker infants, Sai Sunil Kishore et al examined whether infants treated for surfactant deficiency were better supported by NIMV or NCPAP. (37) Seventy-six preterm neonates (mean GA 30.8 weeks, mean birthweight 1,250 g) were randomized to receive NIMV or NCPAP within 6 hours of birth. About 60% of these infants required transient intubation and surfactant administration without mechanical ventilation (ie, the INSURE method). (21) Infants were judged to have failed the assigned treatment, and underwent intubation if they met strict criteria of hypercarbia or apnea within the first 48 hours of treatment allocation. The failure rate in infants randomized to NIMV was less than half the failure rate in infants randomized to NCPAP, (37) suggesting that **NIMV may improve ventilation and decrease apnea compared with NCPAP in sicker infants as well.**

The decreased intubation rate in NIMV-treated infants described earlier supports the idea that NIMV reduces the requirement for mechanical ventilation compared with NCPAP within the first 48 hours after birth. (37) However, in a larger study of 200 infants with RDS with similar mean birthweights and GAs who were randomized to NIMV or NCPAP, Meneses et al found **no significant difference between the groups in the need for intubation and invasive ventilation in the first 72 hours after birth, but the trend favored the NIMV group.** (38) Notably, infants were similarly allowed to receive surfactant using the INSURE method, and a similar proportion of infants in each group (~70%) were given surfactant. (21) Moreover, the criteria for intubation and ventilation were almost identical. A comparison of the NIMV settings in the 2 studies reveals no clinically significant differences except for the NIMV rate—in the Sai Sunil Kishore et al study, the NIMV rate was about double that of the Meneses et al study. It seems unlikely that this

difference in support could underlie the differences in results between the 2 studies. Consequently, the reasons leading to these divergent conclusions are unclear. However, a recent meta-analysis by Meneses et al (39) of 3 randomized controlled studies of NIMV versus NCPAP after birth, including both studies discussed before, (37)(38) estimated a significant decrease in the need for intubation and mechanical ventilation within the first 72 hours of age in infants treated with NIMV compared with NCPAP.

Following a period of invasive ventilation for RDS, many preterm infants are placed on NCPAP to maintain FRC, reduce apnea, and reduce the risk of reintubation and continued invasive ventilation. The risk reduction, however, is only about 60%, (40) raising the question of whether more aggressive noninvasive support can reduce this risk. In fact, a number of randomized, controlled studies provide support for NIMV in this role. Khalaf et al randomized 64 preterm infants with RDS born before 34 weeks' gestation (mean GA 27.7 weeks, mean birthweight 1,061 g) to treatment with NIMV or NCPAP after extubation. Significantly more children in the NIMV group (94%) remained extubated than those in the NCPAP group (60%). (41) In a contemporaneous study, Barrington et al randomized 54 preterm infants with RDS (mean GA 26.3 weeks, mean birthweight 831 g) to receive NIMV or NCPAP following extubation. (42) In this study, infants were intubated for a mean duration of 7.6 days. A higher percentage of infants randomized to NIMV remained extubated (85%) compared with infants randomized to NCPAP (56%). These early studies have been supported by multiple studies since that time. In fact, a recent meta-analysis of 10 randomized, controlled trials and 1,432 infants comparing NIMV with NCPAP after extubation found statistically and clinically significant reductions in the risk of extubation failure in infants treated with NIMV. (43) Accordingly, the discussion herein supports the idea that NIMV decreases the need for invasive ventilation in preterm infants with RDS both early—at the beginning of the hospitalization—and in infants who require invasive ventilation later—after extubation.

Unfortunately, despite this decreased need for invasive ventilation, **the conclusion that use of NIMV fails to reduce long-term pulmonary morbidity is inescapable.** The 2001 study by Barrington et al found no difference in BPD risk between infant groups randomized to NIMV or NCPAP after extubation, (42) and the 2011 study by Meneses et al also found no difference in rates of BPD between these same 2 groups. (38) In their meta-analysis, Meneses et al observed no difference in the incidence of BPD in NIMV-treated infants. (39) Finally, in a large multicenter trial, 1,009 preterm infants with RDS (mean GA 26.1 weeks,

mean birthweight 803 g) were randomized to receive NIMV or NCPAP. The assigned treatment was provided either as primary therapy, or after initial extubation. The same proportion (60%) of infants in the groups underwent reintubation after extubation. No difference was found in the combined incidence of death before 36 weeks' postmenstrual age or the incidence of BPD, or the individual incidences of either death or BPD. (44) Accordingly, although there may be nonpulmonary benefits in treatment with NIMV, including ease of care and parental interaction, the use of NIMV to decrease BPD in preterm infants with RDS is unwarranted.

In the same way that modern synchronized ventilation reduces the magnitude of respiratory support required, (45) NIMV synchronized to an infant's spontaneous breathing may be beneficial. Synchronization occurs through detection of the patient's inspiratory flow at the nares. Preterm infants with RDS receiving synchronized NIMV can display increased respiratory comfort (46) and gas exchange (47) compared with infants receiving nonsynchronized NIMV. However, significant patient-ventilator asynchrony can occur because of weak inspiratory efforts and auto-triggering. (48) The few single-center studies comparing synchronized NIMV with nonsynchronized NIMV have found little difference in outcomes. (49)

## NEURALLY ADJUSTED VENTILATORY ASSIST

In light of the potential benefits of synchronized NIMV, perhaps allowing patients to control all parameters of their noninvasive support may affect long-term pulmonary outcomes. NAVA uses the infant's integrated diaphragmatic activity to determine the onset of the assisted breath, the pressure employed during the breath, and the duration of assist. First used in adults, NAVA uses **an esophageal electrode to measure the electrical activity of the diaphragm** and uses characteristics of this signal to control the ventilator. (50)(51) The ventilator-assisted breath begins when the ventilator detects an increase in diaphragmatic activity greater than the threshold. The delivered pressure increases as a function of the increase in diaphragmatic signal. The magnitude of change in the assist pressure delivered is determined by a multiplier of the instantaneous diaphragmatic signal activity. This multiplier is set by the physician to provide the desired level of pressure support. Following peak diaphragmatic activity, which occurs at the time of peak inspiratory effort, ventilator assist pressure decreases as a function of the decrease in diaphragmatic signal. Once the diaphragmatic activity is 40% to 70% of maximum, inspiratory assist stops and the expiratory phase begins. (52)

Thus, the goal of NAVA is to transduce, on a breath-by-breath basis, the timing and intensity of the patient's own inspiratory effort into synchronous support provided by the ventilator. **NAVA may be provided through an endotracheal tube, or noninvasively, through nasal prongs.** Unlike synchronized NIMV, diaphragmatic activity triggers the ventilator breath and does not depend on patient-driven changes in airflow. (51)

NAVA is used in adult patients to improve patient-ventilator synchrony (53) and reduce overassistance during spontaneous breathing trials. (54) (55) In pediatric patients, a case-control study of 30 pediatric patients in the intensive care unit found that patients who received invasive NAVA demonstrated less agitation, as measured by heart rate and mean arterial pressures, compared with conventional ventilation, and required lower peak inspiratory pressure (PIP). (56) In fact, a systematic review of studies in pediatric patients found that patient-ventilator interaction improves with invasive and noninvasive NAVA, and provides decreased PIP. (57) Finally, Kallio et al randomized 170 pediatric patients to invasive ventilation with NAVA or conventional ventilation. (58) Median ventilator time was not different between the groups. However, when postoperative patients were excluded, significantly less sedation was used during ventilation with NAVA compared with conventional ventilation, suggesting that patient-ventilator interaction and patient comfort were improved. In addition,  $\text{FiO}_2$ ,  $\text{Pco}_2$ , and oxygenation index were all lower in the NAVA group. (58)

In preterm infants, several studies have compared invasive NAVA ventilation with conventional ventilation. The primary conclusions in each were that NAVA ventilation is safe and that PIPs required with NAVA were generally lower than with conventional ventilation. (48)(59)(60) In addition, characteristics of patient-ventilator synchrony such as decreased delay to triggered breath onset, delivered inspiratory time, and inspiratory time in excess of demand were all significantly decreased with NAVA ventilation. (48) Finally, the work of breathing has been found to be improved with NAVA compared with conventional ventilation. (61)

Studies in preterm infants that have compared noninvasive NAVA with other modes of noninvasive ventilation have been few. In a randomized, controlled, observational, crossover study of 11 preterm infants, Gibu et al switched infants on NCPAP, HFNC, or NIMV to noninvasive NAVA for 2- to 4-hour periods. When compared with NIMV, NAVA significantly reduced mean PIP and  $\text{Fio}_2$ . Infants receiving NAVA also exhibited fewer and shorter oxyhemoglobin desaturations. Furthermore, infants receiving NAVA

demonstrated unloading of the respiratory effort. (62) These data suggest that NAVA may improve oxygenation, decrease patient-ventilator asynchrony that results in oxyhemoglobin desaturation, and decrease the work of breathing. Finally, Beck et al evaluated patient-ventilator synchrony through simultaneous measurements of diaphragmatic activity and airway pressure. In this small study, esophageal NAVA electrodes were placed in 7 premature infants receiving conventional ventilation (mean GA 29 weeks) who were close to extubation. Infants briefly received invasive NAVA, then underwent extubation and were given noninvasive NAVA. While receiving noninvasive NAVA, infants had lower respiratory rates and better correlation between diaphragmatic electrical activity and airway pressures than with conventional ventilation. These data suggest that noninvasive NAVA provides equivalent patient-ventilator synchrony to invasive NAVA despite delivering support through a nasal interface. (51)

Although noninvasive NAVA is new, early studies suggest that it is safe and may provide improved synchronization, smaller PIPs, and decreased work of breathing compared

with NIMV. However, the question of whether these effects have any impact on the duration of ventilation or long-term pulmonary outcomes in preterm infants remains uncertain.

## SUMMARY

Table 2 provides direct comparisons of the risks and benefits of NCPAP, HFNC, NIMV, and NAVA in preterm infants with RDS. NCPAP provides monitored distending pressure to the upper airway, lower airways, and lung, and addresses the atelectasis, decreased lung compliance, and increased work of breathing that characterize RDS in the preterm newborn. Care should be taken to ensure that the pressure delivered is not impeded by the resistance of the nasal prongs. HFNC is indicated in the preterm infant with a stable requirement for supplemental oxygen. Because the distending pressure is not monitored, care should be taken to avoid pulmonary overinflation. HFNC is not a replacement for NCPAP, and should not be used to deliver distending pressure. NIMV may be indicated in the preterm infant who requires more distending pressure than is

**TABLE 2. Approaches, Benefits, and Risks of Noninvasive Forms of Respiratory Support for RDS in Preterm Infants**

	APPROACHES	BENEFITS	RISKS
Nasal continuous positive airway pressure	Monitored and controlled positive pressure through nonrestrictive nasal prongs	Improves V/Q mismatch Improves oxygenation Maintains FRC Reduces atelectasis Decreases work of breathing	Nasal trauma Air leak syndromes Gastric distention
High-flow nasal cannula	Heated, humidified flow of supplemental oxygen through small-bore nasal cannula	Parental acceptance Ease of nursing care Reduced gastric distention	Distending pressure is unmonitored and can be dangerously high or ineffective
Nasal intermittent mandatory ventilation	Pressure-regulated, time-cycled positive pressure delivery through restrictive or nonrestrictive nasal prongs Synchronized or nonsynchronized	Improves gas exchange  Improves oxygenation Decreases work of breathing Maintains FRC Decreases need for invasive ventilation	Nasal trauma  Gastric distention Air leak syndromes
Neurally adjusted ventilatory assist	Diaphragm activity-controlled and regulated pressure delivery	Improves patient-ventilator synchrony Improves patient comfort  Reduces peak inspiratory pressures	Limited data regarding efficacy  Limitations in extremely premature infants with immature respiratory rhythm

FRC=functional residual capacity; RDS=respiratory distress syndrome; V/Q=ventilation/perfusion ratio.

practical with NCAP, and may obviate the need for intubation or reintubation. NAVA may be indicated in the preterm infant who requires more distending pressure than is practical with NCAP. NAVA may increase patient-ventilator synchrony and comfort, and allow decreased respiratory support. None of the noninvasive modes of respiratory support has been shown to decrease the risk of BPD in preterm infants despite large studies. Accordingly, noninvasive respiratory support should be considered for clinical goals other than the reduction of BPD.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical strategies and therapies used to decrease the risk and severity of RDS.
- Know the indications for and techniques of continuous positive airway pressure.

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# Index of Suspicion in the Nursery

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## Vomiting and Bradycardia in a Newborn Infant

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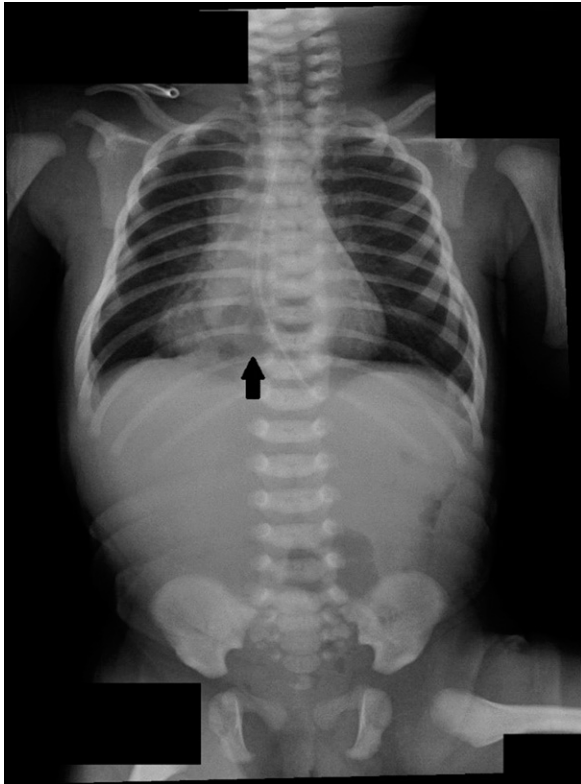
### PRESENTATION

A male infant is born at 39 weeks and 5 days' gestational age via normal spontaneous vaginal delivery to a 21-year-old gravida 1, para 0 woman with no known medical problems. The pregnancy is uncomplicated and prenatal laboratory results are all unremarkable. Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. Initial newborn examination findings are within normal limits. The infant is born with a birthweight of 3.34 kg, head circumference of 32.3 cm, and length of 52.1 cm, with all measurements plotted to be appropriate for gestational age. The infant is noted to be tolerating breast and bottle feeds well and is voiding and passing stools normally. He is discharged from the newborn nursery 2 days after birth with normal physical examination findings and a weight of 3.3 kg, which is 1.2% below birthweight.

Four days after birth, the infant is brought back to the birth hospital for feeding intolerance and having increased nonbloody, nonbilious vomiting with phlegm after each feeding. In the emergency department (ED), the infant is noted to have lost 12% of his birthweight. He is also found to have self-limiting episodes of bradycardia with heart rates in the 70 beats/min range. Electrocardiography is performed, which shows sinus bradycardia. He receives two 10-mL/kg boluses of normal saline, and the heart rate improves to around 100 beats/min with intermittent dips to around 90 beats/min. The infant's other vital signs are otherwise within normal limits for age. A full sepsis evaluation is initiated in the ED and the infant is started on ampicillin and gentamicin treatment for presumed sepsis. The lumbar puncture is unsuccessful, but blood and urine culture specimens are obtained. Rapid testing for respiratory syncytial virus and influenza A and B has negative results and the chest radiograph is normal. Complete blood cell count reveals a white blood cell count of  $8,000/\mu\text{L}$  ( $8.8 \times 10^9/\text{L}$ ), with a normal differential, hemoglobin of 17.6 g/dL (176 g/L), hematocrit of 53.2%, and platelet count of  $409 \times 10^3/\mu\text{L}$  ( $4.09 \times 10^9/\text{L}$ ). The basic metabolic panel is significant for hypernatremia, with a sodium level of 151 mEq/L (151 mmol/L). The sample is hemolyzed and the potassium level is not reported. Other values are within normal limits with chloride of 112 mEq/L (112 mmol/L), total bicarbonate of 22 mEq/L (22 mmol/L), glucose of 73 mg/dL (4.05 mmol/L), blood urea nitrogen of 11 mg/dL (3.9 mmol/L), creatinine of 0.55 mg/dL (48.6  $\mu\text{mol/L}$ ), and calcium of 10.1 mg/dL (2.5 mmol/L).

The infant is transferred to a level III NICU for further evaluation and management. Abdominal radiography is performed on admission to the unit, which shows an overall 'gasless' abdomen and a cystic lucency projecting over the lower mediastinum (Fig 1). He is given nothing by mouth on admission and

**AUTHOR DISCLOSURE** Drs Cheang, Kaur, Haleem, Borole, and Velazquez have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



**Figure 1.** Radiograph depicting a 'gasless' abdomen. The black arrow points to a cystic lucency projecting over the lower mediastinum.

started on intravenous fluids. Pediatric surgery is consulted and computed tomography (CT) of the chest, abdomen, and pelvis is completed, which shows a complex gastric hernia with the gastroesophageal junction above the diaphragm (Fig 2). A subsequent barium esophagography confirms a hiatal hernia or intrathoracic stomach with significant partial obstruction (Fig 3). Echocardiography is also performed, which shows a structurally normal heart with good function but an external impingement on the posterior aspect of the left atrium is noted.

A diagnosis of a hiatal hernia with compression of the heart is made, which is likely the factor contributing to the episodic bradycardia. The infant is taken to the operating room 8 days after birth for open repair of the hiatal hernia with gastrostomy tube placement. A gastrostomy is placed to provide support or hold the stomach to the anterior abdominal wall. Intraoperatively, the infant is found to have a small diaphragmatic defect and a large portion of the proximal stomach in the chest, with only the distal stomach and pylorus in the thoracic cavity. The stomach is reduced and the hiatal defect is repaired with crural approximation.

The infant has no postoperative complications and is able to tolerate ad libitum feeds by mouth before discharge on postoperative day 6. No further episodes of vomiting or

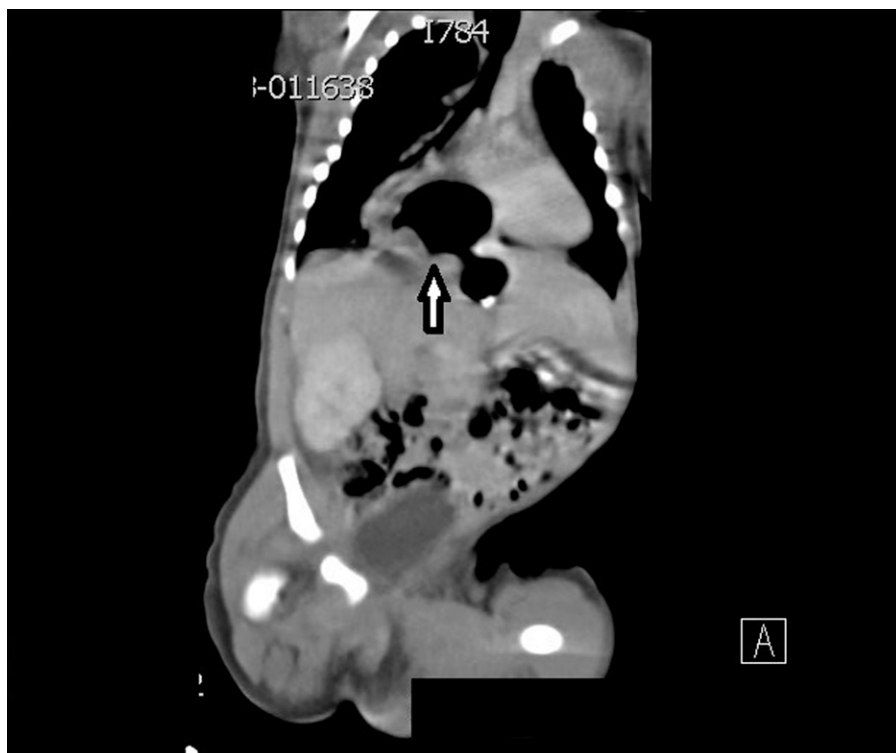
bradycardia are noted and he demonstrates appropriate weight gain. The infant is discharged from the hospital with instructions to the family to follow up with pediatric surgery 2 months later. On outpatient follow-up, he continues to gain weight appropriately, and the gastrostomy was reversed successfully without complications.

## DISCUSSION

Congenital hiatal hernias are very rarely seen in the neonatal period and are characterized by a herniation of the abdominal organs, most commonly the stomach, into the thorax from a physiologic opening caused by the laxity of the attachment of the stomach and gastroesophageal junction. Congenital hiatal hernia has to be distinguished from the congenital diaphragmatic hernia, which is a separate entity where there is a pathologic defect in the diaphragm. There are 4 anatomic classifications of hiatal hernias, types I, II, III and IV. Type I or a sliding-type hernia is the most common type, accounting for more than 90% of cases. (1) Type II or a paraesophageal-type hernia, although considered a rarer type, has a higher risk of complications such as incarceration, strangulation, complete gastric herniation with organo-axial volvulus, and a perforation of herniated viscera. (2)(3) Type III is a combination of type I and II, and type IV is characterized by the presence of a structure other than the stomach, such as the omentum, colon, or small bowel within the hernia sac. (1)

Congenital hiatal hernias may present with symptoms such as respiratory distress, vomiting, poor feeding, failure to thrive, poor feeding, or signs such as bradycardia as observed in the current case when the hernia is massive enough to cause cardiac compression. These signs and symptoms have a broad list of differential diagnoses including sepsis, gastroesophageal reflux disease, pneumonia, pneumatocele, pneumothorax, pleural effusion, and congenital diaphragmatic hernia. The diagnosis of hiatal hernias is usually made with a barium swallow esophagography, upper endoscopy, or CT scan showing the herniation of intra-abdominal contents into the thorax. (1)

Although rare, there have been 9 reported cases of congenital hiatal hernia diagnosed antenatally. (4)(5)(6)(7)(8)(9) All of the reported cases were identified during the third trimester of pregnancy. It is postulated that the late onset of findings is because of the fact that the fetus may only be able to develop sufficient pressure to dilate the intrathoracic stomach by the third trimester. Hence, with the development of adequate pressure during swallowing and likely with the effect of reflux of gastric secretions into the esophagus, the dilated esophagus/stomach may be



**Figure 2.** Computed tomography scan of the chest, abdomen, and pelvis with the white arrow pointing to a gastric hernia with the gastroesophageal junction above the diaphragm.

visualized during third-trimester ultrasonography. (8) This finding has been described as a presence of a cystic mass in the posterior mediastinum, usually located behind the heart juxtaposed to the vertebral body and connecting to the intra-abdominal stomach. (7)

Surgical correction is the treatment of choice, especially in symptomatic paraesophageal hernias with obstructive symptoms. Patients may also be asymptomatic; however, because of the risk of subsequent complications, elective surgical treatment is necessary shortly after diagnosis. (10)



**Figure 3.** Barium esophagram confirming a hiatal hernia with the black arrows pointing to an intrathoracic stomach with significant partial obstruction.

#### Lessons for the Clinician

- Although rare, congenital hiatal hernia should be considered in a neonate with gastrointestinal symptoms, such as vomiting, and respiratory distress.
- Early diagnosis and surgical treatment are important to prevent complications and morbidity of hiatal hernia such as aspiration pneumonitis, gastric ulcers, gastric dilation, perforation, gangrene, and ultimately, cardiopulmonary arrest.

### American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the morphogenesis of the GI tract and factors that lead to congenital malformations.

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## Case 1: Vomiting and Bradycardia in a Newborn Infant

Stefanie Cheang, Rupinder Kaur, Sadia Haleem, Swapna Borole and Danitza Velazquez

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# Index of Suspicion in the Nursery

## 2 Rapidly Growing Neck Mass in an Extremely Preterm Infant with Pulmonary Hypertension

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### PRESENTATION

A male infant is born at a gestational age of 27 weeks, 4 days via cesarean delivery to a 27-year-old gravida 2, para 1 woman with severe preeclampsia (treated with intravenous magnesium and nifedipine). The pregnancy had been complicated by systemic lupus erythematosus (treated with prednisone and plaquenil) and type 2 diabetes (treated with insulin and aspirin). Second-trimester prenatal ultrasonography at 25 weeks' gestation reveals intrauterine growth restriction with an estimated fetal weight less than the 3rd percentile. At delivery, the infant's Apgar scores are 5 and 8 at 1 and 5 minutes, respectively. He receives positive pressure ventilation, makes a transition to continuous positive airway pressure (CPAP) of 5 cm H<sub>2</sub>O, and is transported to the NICU.

During his NICU stay, the infant develops severe bronchopulmonary dysplasia with pulmonary hypertension, apnea and anemia of prematurity, retinopathy of prematurity, failure to thrive, and postnatal growth restriction. Forty-four days after birth, he starts treatment with sildenafil 1 mg/kg per dose every 8 hours for pulmonary hypertension. Fifty-eight days after birth, soft, nonblanching skin-colored nodules develop in both axillae and supraclavicular fossae, but are more prominent on the right side (Fig 1).

An apparent palpable thrill is detected in the axillary lesions, leading to a clinical diagnosis of hemangioma. Of note, there is no laboratory or clinical evidence of consumptive coagulopathy (white blood cell count 8,200/ $\mu$ L [ $8.2 \times 10^9$ /L], hemoglobin 9.8 g/dL [98 g/L], hematocrit 31.5%, platelet count 398  $\times 10^3$ / $\mu$ L [ $398 \times 10^9$ /L], prothrombin time 12.3 seconds, international normalized ratio 1.2, partial thromboplastin time 36.2 seconds, and fibrinogen 214 mg/dL [2.14 g/L]).

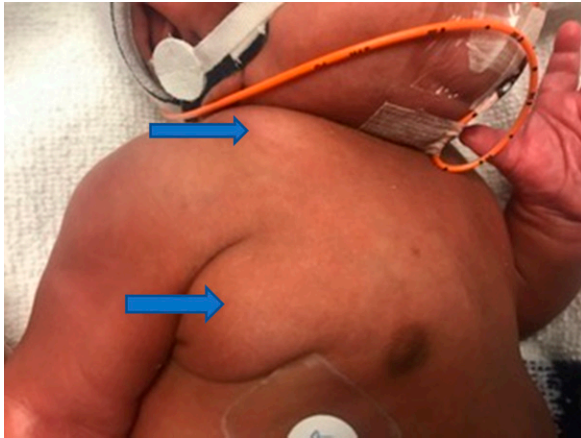
Ultrasonography of the neck (Fig 2) demonstrates an infiltrative echogenic lesion in both axillae containing vessels that demonstrate both arterial and venous flow.

Chest radiography demonstrates no intrathoracic extension and no airway compromise.

Magnetic resonance imaging with contrast is performed to further characterize the axillary masses. It demonstrated slightly enhancing ill-defined lobular axillary lesions extending to the base of the neck.

Given the presumed diagnosis of hemangioma and an observed interval enlargement of the lesions, treatment with propranolol is started. After 3 weeks, no clinical change is noted in the lesions and propranolol is discontinued.

**AUTHOR DISCLOSURE** Drs Pattnaik, Levin, Gagne, and Angert have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



**Figure 1.** Photograph of the infant demonstrating a right-sided neck mass (arrow). This was present on the left side of the neck as well and extended into the axillae.

A contrast-enhanced computed tomography (CT) scan (Fig 3) reveals prominent low attenuation tissue in the lower neck, supraclavicular region, and axilla bilaterally. No discrete mass is identified and faint postcontrast enhancement is noted. A diagnosis of prominent brown adipose tissue is made.

Echocardiography performed 85 days after birth reveals improved right ventricular pressures with persistent elevation of right ventricular pressure with sildenafil treatment to less than half the systemic pressure. The neonate's respiratory needs improve with progressive weaning of CPAP. On 114 days after birth, he is transferred to an inpatient rehabilitation facility receiving treatment with sildenafil and CPAP 7 cm H<sub>2</sub>O, and 23% oxygen for respiratory support. He is weaned off CPAP before discharge 157 days after birth, when he was sent home with nasal cannula oxygen.

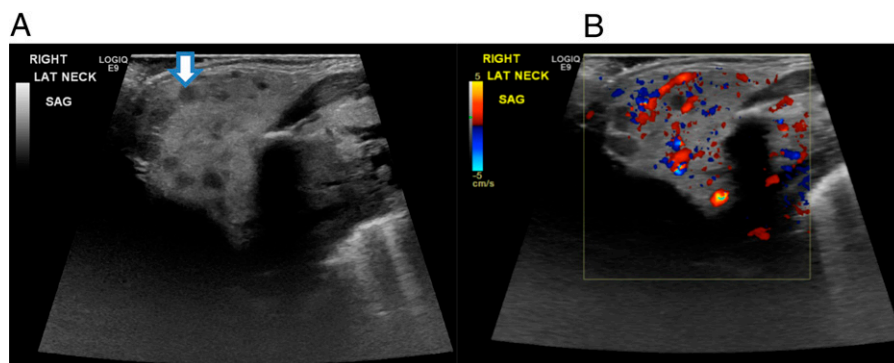
## DISCUSSION

Brown adipose tissue (BAT) is rich in glycogen, cholesterol, and phospholipids. In contrast to white adipose

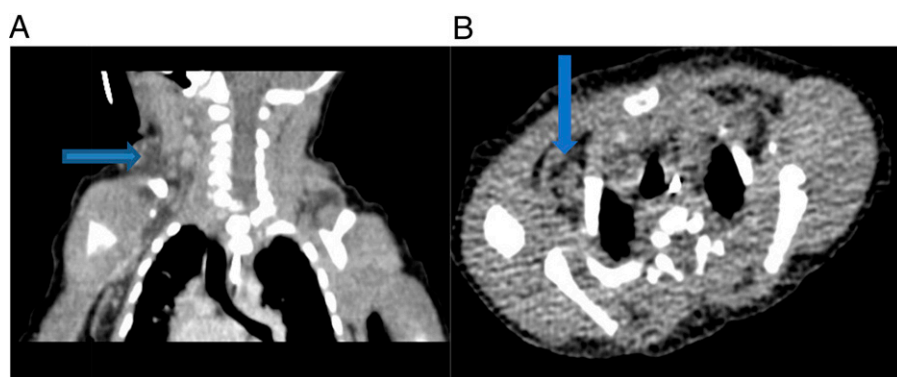
tissue, which stores energy, brown fat is involved in nonshivering thermogenesis. (1) This ability is dependent on the expression of uncoupling protein 1 (UCP1), a mitochondrial protein transporter that uncouples electron transport from adenosine triphosphate production. (2) UCP1, which is unique to brown fat, is activated via a signaling cascade triggered by norepinephrine. In humans, brown adipose tissue typically accumulates within the neck, axillae, back, subpleural regions, mediastinum, abdomen, and thigh, and is more abundant in the fetus and neonate, where it may constitute approximately between 1% and 5% of body weight. (3) At 8 weeks after birth, the amount of BAT gradually declines. In adults, it may still be found in the perirenal space, posterior cervical and axillary lymph nodes, and intercostal areas. (4)

In the current case, masslike areas developed, which proved to represent BAT, after treatment with sildenafil for pulmonary hypertension. The relationship between sildenafil and BAT has been previously reported in overweight adults. It has been shown that sildenafil induces the development of brown fat by causing an increase in multilocular UCP1-positive adipocytes and the expression of UCP1 protein and mRNA. Sildenafil also increases mitochondrial density. (5) The mechanism of brown fat induction by sildenafil was proposed by Li et al. (5) Sildenafil increases plasma cyclic guanosine monophosphate and catecholamine, and consequently activates the mammalian target of rapamycin and protein kinase G/vasodilator-stimulated phosphoprotein signaling pathways, respectively, which may be responsible for brown fat activation.

In conclusion, the development of axillary and neck masses in a child with pulmonary hypertension treated with sildenafil should prompt consideration of the diagnosis of brown fat proliferation. Ultrasonography may



**Figure 2.** Ultrasound scan of the right side of the neck without (A) and with (B) color Doppler shows an infiltrative echogenic lesion containing multiple rounded hypodense areas (arrow). Doppler image demonstrates prominent vascular flow within the mass.



**Figure 3.** Contrast-enhanced coronal (A) and axial (B) computed tomography scan of the neck shows low attenuation tissue in the lower neck extending to both axillae consistent with fat (arrows). No additional mass was identified.

demonstrate echogenic tissue characteristic of brown fat. Although it was not performed in the current case, positron emission tomography (PET)/CT may be useful in confirming the diagnosis. Radiotracer from PET/CT using fludeoxyglucose  $^{18}$ F readily accumulates in sites of metabolically active BAT.

#### Lessons for the Clinician

- Brown fat proliferation can be associated with sildenafil use in neonates and it is benign.
- Other causes of highly vascular masses in the neck and axilla, such as hemangioma, hemangioendothelioma, and arteriovenous malformations or lipoblastoma should be considered in the differential diagnosis.
- Ultrasonography of the neck is the initial choice of imaging study, and magnetic resonance imaging or positron emission tomography can help confirm the diagnosis in difficult cases.

### American Board of Pediatrics Neonatal-Perinatal Content Specification

- Normal development of the nose, mouth, throat, and neck.

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## Case 2: Rapidly Growing Neck Mass in an Extremely Preterm Infant with Pulmonary Hypertension

Priyam Pattnaik, Terry Levin, Samuel Gagne and Robert Angert

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# Index of Suspicion in the Nursery

## 3 A Rare Cause of Respiratory Distress and Excessive Salivation in a Term Infant

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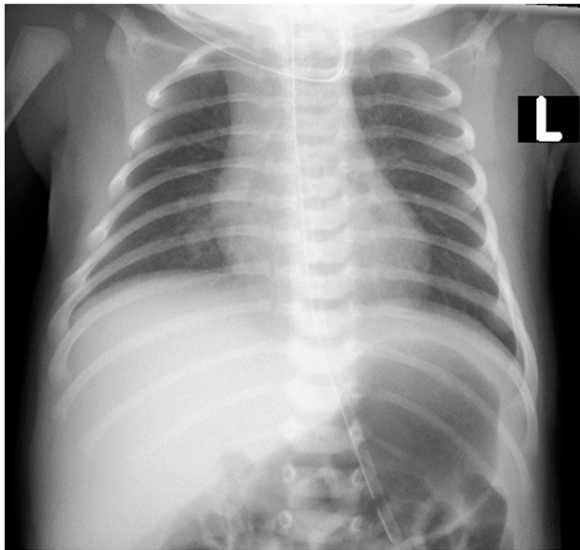
### PRESENTATION

A female infant is born at 39 weeks' gestation via normal vaginal delivery to a 22-year-old primigravida woman. The woman's pregnancy had been uncomplicated. Antenatal ultrasonography findings are normal. Results of her perinatal toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH) infection tests are negative, and group B *Streptococcus* screening result is negative. The membranes rupture just before delivery. Significant finding at delivery includes a meconium-stained amniotic fluid. The infant is vigorous at birth, with Apgar scores of 7 and 9 at 1 and 9 minutes, respectively, and a birthweight of 3,550 kg. She is sent to the normal nursery with her mother in good condition; 2 hours after birth, she develops respiratory distress with desaturation, and is immediately transferred to the NICU for further evaluation and treatment.

The infant is given continuous positive airway pressure of 5 cm H<sub>2</sub>O. Fraction of inspired oxygen (Fio<sub>2</sub>) is 50%; temperature 36.8°C; heart rate 130 beats/min; respiratory rate 70 breaths/min; and oxygen saturation 94%. Her blood pressure is 73/49 mm Hg.

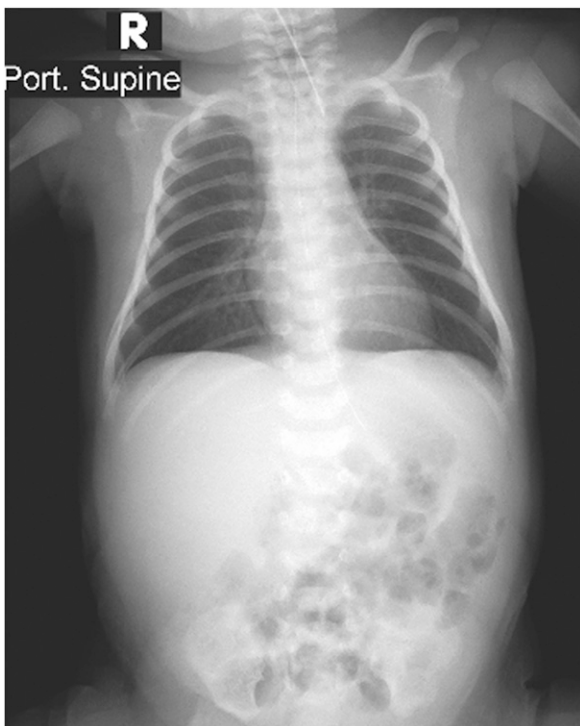
On physical examination, she is awake and alert, has no dysmorphic features, and chest examination shows respiratory distress with intercostal retractions and diffuse inspiratory and expiratory wheezing. She is also noted to have excessive salivation. No significant organomegaly is found on abdominal examination, and the rest of the systemic examination findings are within normal limits. A blood culture specimen is obtained, and empiric treatment is started with ampicillin and gentamicin. Initial blood gas measurement reveals respiratory acidosis: pH 7.18, Pco<sub>2</sub> 69 mm Hg (9.18 kPa), and bicarbonate 25 mEq/L (25 mmol/L); radiography reveals proper lung inflation and no lung opacities (Fig 1). Over the next hour, she continues to require oxygen to maintain her oxygen saturation above 90%. She develops severe respiratory distress and worsening of the respiratory acidosis on blood gas measurement (pH 7.14, Pco<sub>2</sub> 78 mm Hg [10.3 kPa], bicarbonate 26 mEq/L [26 mmol/L]). She undergoes intubation and receives mechanical ventilation. After intubation, her blood gas measurements improve and radiography reveals no significant changes; the endotracheal tube (ETT) is in a good position (at a depth of 8.5 cm) (Fig 2), but clinically she is noted to have persistence of deep subcostal retraction and diffuse wheezing. Her

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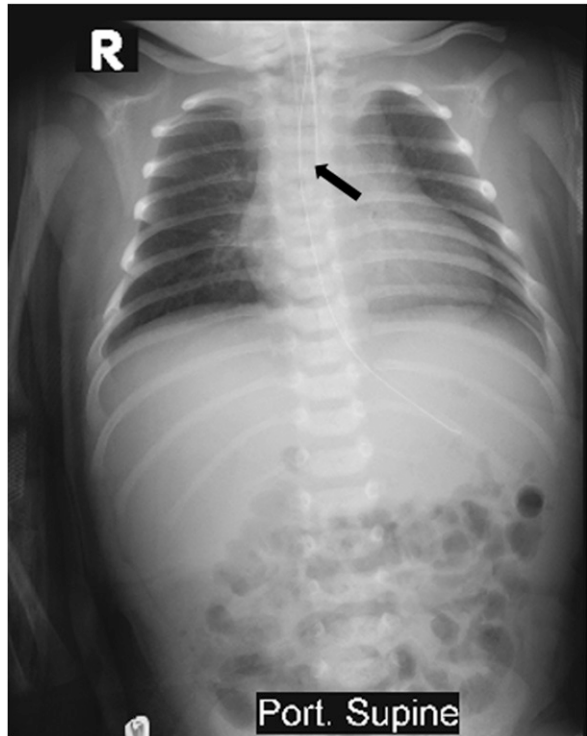


**Figure 1.** First chest radiograph with the patient receiving continuous positive airway pressure revealed proper lung inflation and no lung opacities.

oxygen requirement is increased to 100% to keep saturation above 94%, increased sedation is tried with no improvement, and the infant undergoes reintubation. Clinically she improves after reintubation with better work of breathing, resolution of subcostal retraction and



**Figure 2.** Proper lung inflation and no lung opacities noted after intubation.



**Figure 3.** Proper lung inflation and deep endotracheal tube (arrow) noted after intubation.

wheezing, and significant improvement in oxygen saturation ( $\text{FiO}_2$  21% and saturation 100%); follow-up post-reintubation radiography reveals deep ETT (at a depth of 10 cm, just above the carina; Fig 3).

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute respiratory distress in a newborn with normal radiography findings includes the following:

- Double aortic arch
- Laryngeal web
- Laryngomalacia
- Sepsis
- Subglottic stenosis
- Tracheal stenosis
- Tracheomalacia

## CASE PROGRESSION

After reintubation, an attempt to adjust the ETT position resulted in demonstrations of severe respiratory distress and significant desaturation. So the ETT was kept at the level of the carina, which raised the suspicion of airway

obstruction at the level of distal trachea. A cardiologist was called, and echocardiography did not suggest a cardiac abnormality or obstruction.

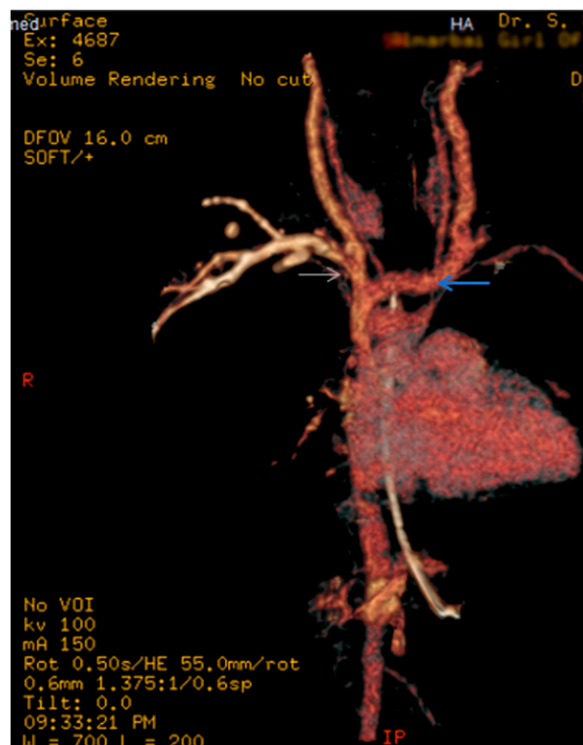
On consultation, pediatric pulmonology recommended computed tomography (CT) angiography with 3-dimensional reconstruction, which confirmed the diagnosis.

## ACTUAL DIAGNOSIS

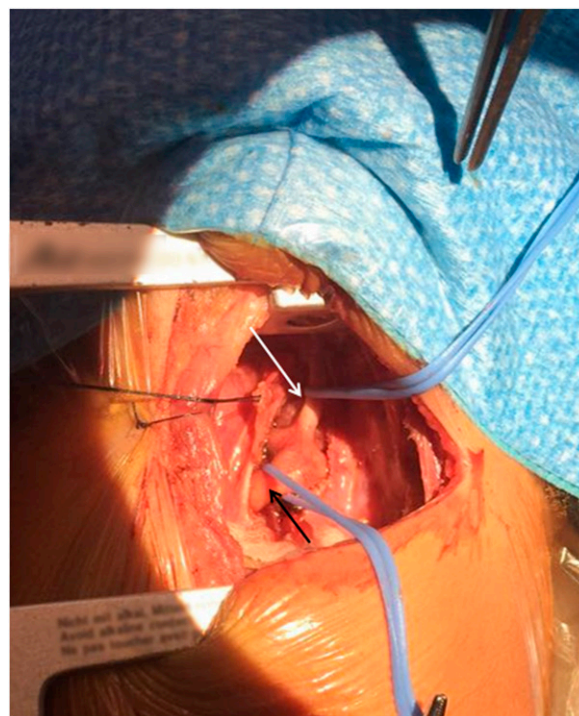
A diagnosis was made of double aortic arch (DAA) with the right arch more prominent and dominant, and the esophagus and trachea completely encircled (Fig 4). The case was referred to a cardiothoracic surgeon, and surgical repair (Fig 5) was undertaken on day 6 after birth. The nondominant left arch and the patent ductus arteriosus were divided. The patient underwent extubation on the second day after surgery. She started feeding on the third day after surgery, and gradually tolerated full oral intake and was discharged in stable condition 12 days after surgery.

## DISCUSSION

DAA is a rare disorder, and it remains an essential element of the differential diagnosis of neonatal respiratory distress.



**Figure 4.** Computed tomography angiography showed a double aortic arch, with a more prominent and dominant right arch (blue arrow) and a non-dominant left arch (white arrow), and the esophagus and trachea completely encircled.



**Figure 5.** The white arrow is pointing to left subclavian artery (LSCA), and black arrow to the patent ductus arteriosus (PDA). The right arch runs behind the esophagus and trachea and is difficult to visualize. The vessel between LSCA and PDA is the left arch, which is surgically divided.

Congenital heart disease occurs in about 1% of neonates, (1) whereas vascular rings occur in about 1 in 10,000 births. (2) The DAA variants are named based on the size of the aortic arch, with right dominant arch seen more frequently (80%) than left dominant or codominant arches (10% each). (3)

Presentation in the neonatal period is rare, and early diagnosis is difficult because it has a broad clinical spectrum. The mean age at diagnosis for the vascular ring is 6 months. (4) The DAA occurs as a result of failure of regression and persistence of bilateral fourth aortic arches and the dorsal aortic root. (3) Some genetic syndromes are associated with higher rates of vascular rings, including coloboma, heart defects, atresia choanae (also known as choanal atresia), growth restriction, genital abnormalities, and ear abnormalities (CHARGE) syndrome, Down syndrome, and DiGeorge syndrome. (5)

The clinical presentation is related to compression of the esophagus and/or trachea. This can include feeding difficulties, excessive salivation, vomiting, stridor, or respiratory distress.

Evaluation of neonates with respiratory distress often proceeds in a stepwise manner similar to the case presented herein; the clue to tracheal obstruction in the

current case was related to significant clinical and blood gas improvement with deep ETT position, just above the carina, and worsening of the respiratory status after adjustment of the tube position, that is, when the tip of the ETT was placed distal to the obstruction.

The diagnosis was confirmed on CT angiography of the chest. When a definitive diagnosis cannot be made on echocardiography, the definitive management for DAA is a surgical correction through surgical ligation of a duplicated arch. Long-term outcomes for neonates with isolated DAA are excellent. The most common postoperative finding is persistent tracheomalacia, which improves in the first few months of age.

#### Lessons for the Clinician

- Respiratory distress and excessive salivation at birth or soon after should alert the neonatologists to the possibility of tracheal and esophageal compression by the vascular ring.
- The presence of symptoms after intubation despite the satisfactory position of the endotracheal tube with no lung disease leads to a high index of suspicion. Symptoms of airway compression secondary to double aortic arch may be relieved by placing an endotracheal tube just above the carina, which can be an essential tool to relieve airway obstruction. When echocardiography is unable to diagnose double aortic arch, alternative tools such as computed tomography angiography must be applied.
- Surgical treatment is useful with an excellent prognosis.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the anatomy and pathophysiology (including genetics) of a neonate with an arterial vascular abnormality.
- Recognize the clinical features of a neonate with an arterial vascular abnormality.
- Know the evaluation and medical and/or surgical management and associated potential complications or adverse effects of such management for a neonate with an arterial vascular abnormality.
- Formulate a differential diagnosis for a neonate with an arterial vascular abnormality.
- Recognize the laboratory, imaging, and other diagnostic features of a neonate with an arterial vascular abnormality.

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### Case 3: A Rare Cause of Respiratory Distress and Excessive Salivation in a Term Infant

Jubara Alallah, Abdulaziz Alkhotani, Ghassan Baslaim and Zanoubia Darwich

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## Premature Preterm Rupture of Membranes and Fetal Decelerations

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

**AUTHOR DISCLOSURE** Drs de los Reyes and Tran have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - o Normal: ≤5 contractions in 10 minutes
  - o Tachysystole: >5 contractions in 10 minutes

#### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

- Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
    - Bradycardia not accompanied by absent variability
    - Tachycardia
    - Minimal or marked baseline variability
    - Absent variability without recurrent decelerations
    - Absence of induced accelerations after fetal stimulation
    - Recurrent variable decelerations with minimal or moderate variability
    - Prolonged decelerations
    - Recurrent late decelerations with moderate variability
    - Variable decelerations with other characteristics, such as slow return to baseline
  - Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
    - Absent variability with any of the following:
      - Recurrent late decelerations
      - Recurrent variable decelerations
      - Bradycardia
    - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists.

Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## CASE PRESENTATION

### History

A 37-year-old, gravida 8, para 3-0-4-3 woman presented with premature preterm rupture of membranes (PPROM) at 28 1/7 weeks' gestation. The pregnancy was notable for advanced maternal age with a low-risk finding on quadruple screen and maternal obesity (body mass index 37 kg/m<sup>2</sup>). Her obstetric history included 3 uncomplicated term spontaneous vaginal deliveries, 2 therapeutic abortions, and 2 first-trimester spontaneous abortions. Her medical, surgical, and family histories were otherwise unremarkable. She was a former smoker who quit smoking before pregnancy.

Upon presentation to the labor and delivery department, she reported leaking of copious clear fluid and was confirmed to have PPRM with positive pooling, ferning, and nitrazine. Her cervix was visually closed and she had no signs or symptoms of preterm labor, abruption, or chorioamnionitis. The FHR pattern was appropriate for gestational age (Fig 1). Ultrasonography demonstrated an appropriate-for-gestational age fetus (estimated fetal weight 889 g [22nd percentile]), breech presentation, and normal amniotic fluid index (21.2 cm). In this setting, she was admitted to the inpatient antepartum service and received expectant management. She received magnesium sulfate for 12 hours for fetal neuroprotection, latent antibiotics for 7 days as per the protocol described by Mercer et al, (1) and betamethasone.

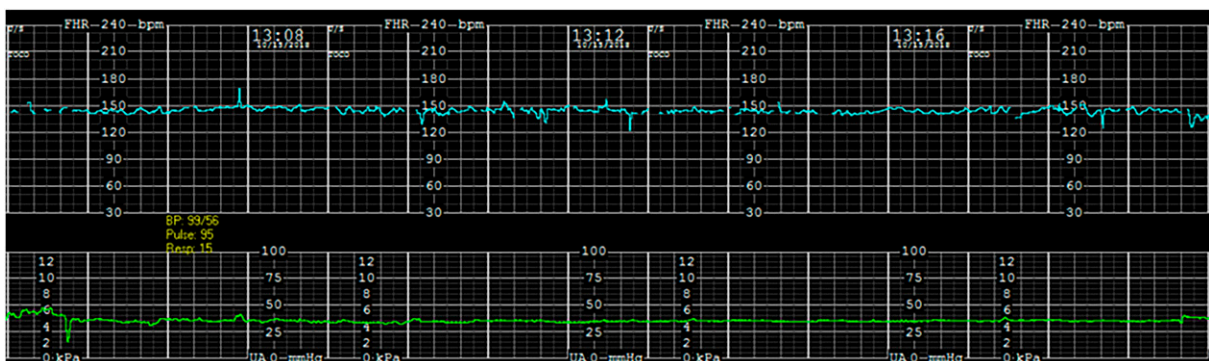


Figure 1. Electronic fetal monitoring strip 1.

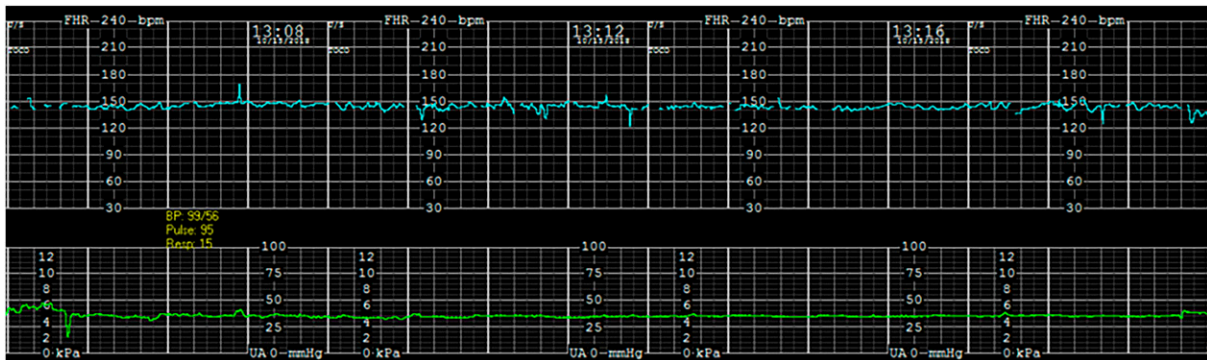


Figure 1. Electronic fetal monitoring strip 1.

Figure 1. Findings from EFM strip 1 are as follows:

- Variability: Moderate
- Baseline rate: 145 beats/min
- Episodic pattern: None
- Uterine contractions: None
- Interpretation: Category I
- Differential diagnosis: Fetus with magnesium exposure, normal acid-base status
- Action: Continued observation

During her antepartum course, she underwent daily fetal heart monitoring which continued to be appropriate for

gestational age. She was diagnosed with gestational diabetes during her admission and her glucose levels were controlled with diet modification.

She remained stable until 32 weeks and 4 days of gestation when she reported increasing intermittent abdominal tightening and back discomfort. The EFM finding was reviewed and new spontaneous decelerations with contractions were noted (Fig 2). Bedside ultrasonography confirmed that the fetus was cephalic at that time. Given her new decelerations—which persisted throughout the day—and worsening symptoms, the obstetrical team recommended induction of labor.

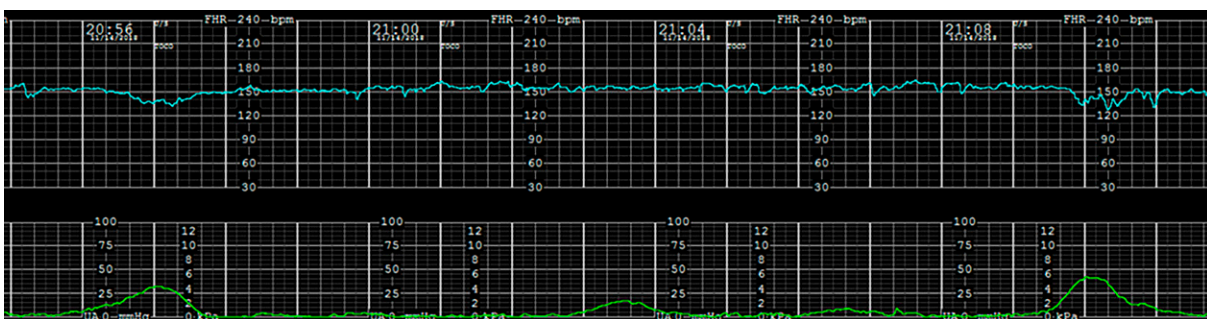


Figure 2. Electronic fetal monitoring strip 2.



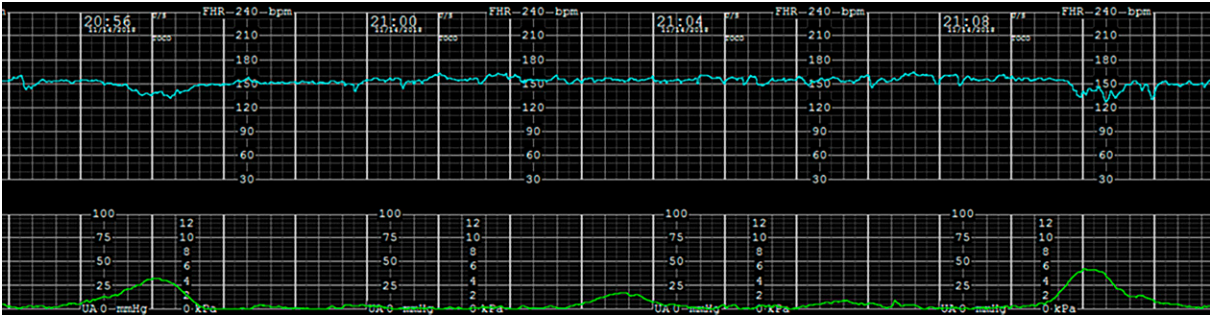


Figure 2. Electronic fetal monitoring strip 2.

Figure 2 Findings from EFM strip 2 are as follows:

- Variability: Moderate
- Baseline rate: 150 beats/min
- Episodic pattern: None
- Periodic pattern: Occasional early and variable decelerations with contractions, 2 in 20 minutes
- Uterine contractions: Regular, every 7 minutes lasting 1 minute each
- Interpretation: Category II
- Differential diagnosis: Fetal head compression, potential uteroplacental insufficiency, umbilical cord compression

- Action: Recommended induction of labor

Her initial sterile vaginal examination showed a closed cervix without any evidence of cord prolapse and she began receiving oxytocin for induction. She received a maintenance dose of intravenous insulin given her diagnosis of gestational diabetes. The oxytocin was titrated per protocol but was discontinued at 3 mL/hour secondary to recurrent variable and late decelerations (Fig 3). Her repeat sterile vaginal examination showed 3-cm dilation and 90% effacement.

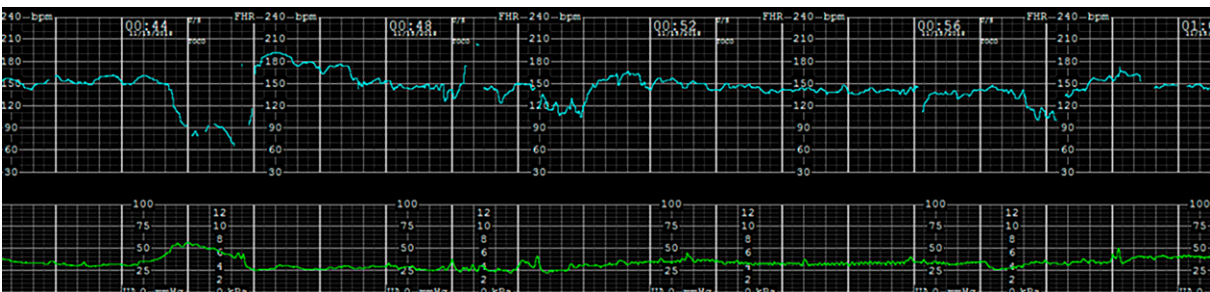


Figure 3. Electronic fetal monitoring strip 3.



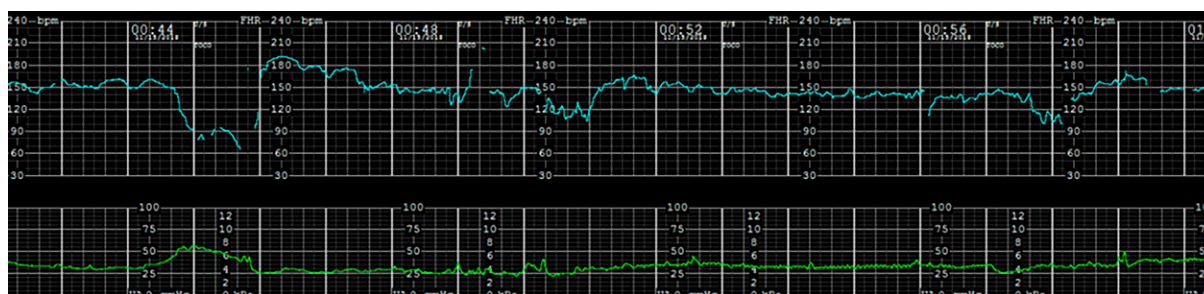


Figure 3. Electronic fetal monitoring strip 3.

Figure 3 Findings from the EFM strip 3 are as follows:

- Variability: Moderate
- Baseline rate: 145 beats/min
- Episodic pattern: None
- Periodic pattern: Variable deceleration with nadir to 70 beats/min, late decelerations with nadir to 100 beats/min
- Uterine contractions: Irregular, difficult to trace given maternal body habitus, inverted at times on tocometry
- Interpretation: Category II

- Differential diagnosis: Placental insufficiency/hypoperfusion, umbilical cord compression
- Action: Oxytocin discontinued, maternal repositioning and hydration with improvement in decelerations

Although the FHR tracing initially improved with maternal repositioning, the fetus subsequently developed more severe, recurrent variable decelerations but with preserved moderate variability and quick return to baseline (Fig 4). Repeat sterile vaginal examination 30 minutes after her last examination was notable for progression to 5 cm dilation.

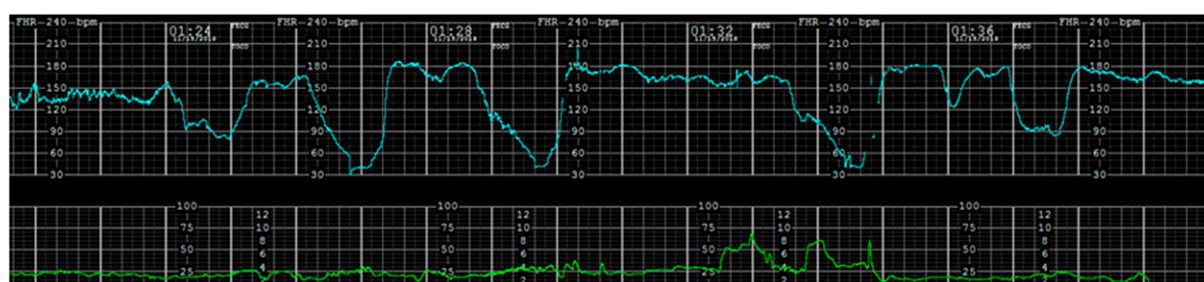


Figure 4. Electronic fetal monitoring strip 4.

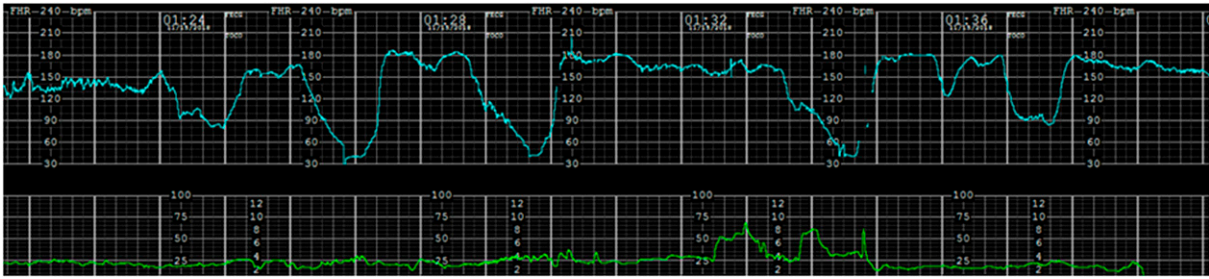


Figure 4. Electronic fetal monitoring strip 4.

Figure 4 Findings from EFM strip 4 are as follows:

- Variability: Moderate
- Baseline rate: 145–155 beats/min
- Episodic pattern: None
- Periodic pattern: Recurrent deep variable decelerations to 40 beats/min
- Uterine contractions: Unable to determine secondary to maternal body habitus, palpation required, contractions corresponded to variable decelerations by palpation

- Interpretation: Category II
- Differential diagnosis: Umbilical cord compression, uterine tachysystole, abnormal umbilical cord insertion
- Action: Patient repositioned

With repositioning, the tracing again improved. Given her quick progression and reassuring tracing after repositioning (Fig 5), expectant management was continued and she soon became fully dilated.

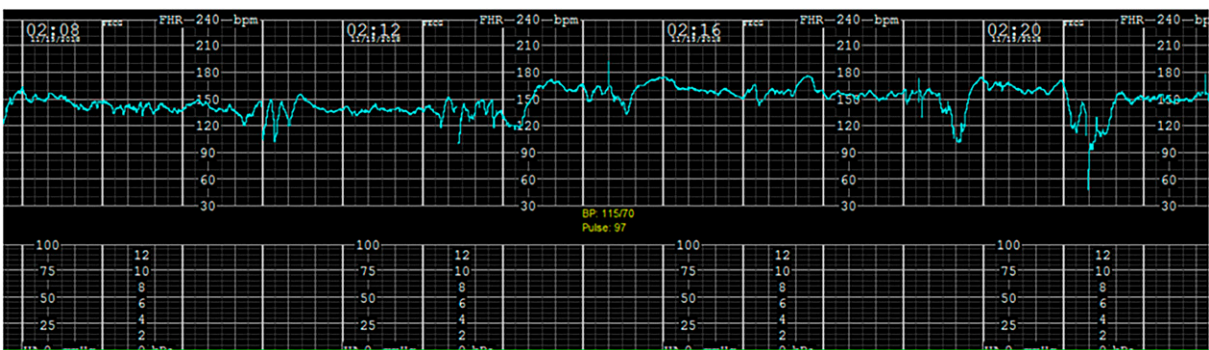


Figure 5. Electronic fetal monitoring strip 5.

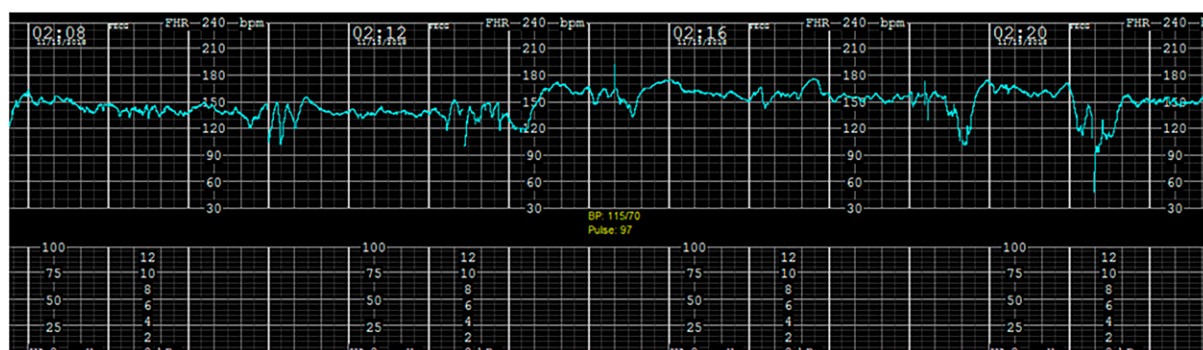


Figure 5. Electronic fetal monitoring strip 5.

Figure 5 Findings from EFM strip 5 are as follows:

- Variability: Moderate
- Baseline rate: 145 beats/min
- Episodic pattern: Occasional variable decelerations
- Periodic pattern: None
- Uterine contractions: Unable to determine, palpation required
- Interpretation: Category II
- Differential diagnosis: Umbilical cord compression, uterine tachysystole, abnormal umbilical cord insertion
- Action: Became fully dilated, pushed to delivery quickly

## Outcome

The patient delivered a female infant at 32 weeks and 4 days' gestational age over an intact perineum. The neonate weighed 1,585 g (29th percentile) and had Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. The neonatology team was present at delivery. The umbilical artery cord blood gas measurements were as follows: pH 7.22,  $P_{CO_2}$  62 mm Hg,  $P_{O_2}$  23 mm Hg, and base excess  $-4$ . The umbilical venous cord gas findings were as follows: pH 7.32,  $P_{CO_2}$  47 mm Hg,  $P_{O_2}$  34 mm Hg, and base excess  $-2$ .

The neonate was admitted to the NICU for prematurity. She did not require respiratory support and received ampicillin and gentamicin, which was discontinued when the 48-hour blood culture had no growth. Feedings were advanced, no additional respiratory support was required, and the infant was discharged from the hospital 12 days after birth.

The placental pathology was notable for severe chorioamnionitis with findings consistent with necrotizing funisitis. Possible thrombi were noted in the fetal vessels along with a hypercoiled cord.

## DISCUSSION

PPROM affects approximately 3% of the general pregnant population in the United States. (2) PPRM is associated

with increased rates of intra-amniotic infection, placental abruption, cord prolapse, stillbirth, and preterm labor. Risk factors include, but are not limited to, history of PPRM, history of prior preterm labor, drug use, smoking, and bleeding. (3) Abnormal FHR tracings are often an indication for delivery because they can offer insight into underlying pathology. (4) Close clinical surveillance for infection, abruption, and preterm labor is important in assessing the health of the in utero environment and determining if the patient is appropriate for ongoing expectant management, as these would be contraindications. (5)

Management options are dependent on gestational age but broadly, after viability, inpatient management is recommended with daily assessment of fetal well-being. (6) A course of latency antibiotics is recommended for prolongation of pregnancy and reduction of morbidity. (1) In addition, a course of steroids is recommended for eligible patients to reduce neonatal mortality and morbidity with some additional evidence that late preterm steroids may also improve neonatal outcomes. (7)(8) Although recent evidence suggests conflicting neonatal data with prolongation of pregnancy beyond 34 weeks 0 days gestational age, the current recommendation is to deliver by 34 weeks 0 days for those with PPRM. (6)(9) A cesarean section should be performed for obstetric indications such as malpresentation, nonreassuring EFM, arrest of labor, or unstable abruption.

In the case of this patient, the final placental pathology was consistent with longstanding intra-amniotic infection in the setting of PPRM. This may have contributed to the chronic inflammatory picture of the placenta and the thrombi noted in the cord. These postnatal histopathologic findings in the umbilical cord and placenta correlate well with the deep variable decelerations (cord compression/blockage) and late decelerations (uteroplacental insufficiency) noted during this patient's labor course. These findings also highlight the limited sensitivity of clinical assessment in detecting chorioamnionitis and the

importance of EFM in providing additional insights into changes in fetal status in the setting of PPROM. As seen in this case, new decelerations in the FHR tracing in a patient with PPROM may be indicative of a significant change in fetal well-being, such as chorioamnionitis, and warrant close attention by clinicians.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes, complications, and management of preterm premature rupture of membranes.

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## ANSWER KEY FOR APRIL 2019 NEOREVIEWS

**Prevention of Bronchopulmonary Dysplasia: A Summary of Evidence-Based Strategies:** 1. B; 2. D; 3. A; 4. E; 5. E  
**Neonatal Respiratory Support on Transport:** 1. E; 2. D; 3. A; 4. C; 5. D.

## Strip of the Month: Premature Preterm Rupture of Membranes and Fetal Decelerations

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## Was the Adverse Outcome from Goldenhar Syndrome or Hypoxic-Ischemic Events?

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A 3,765-g male infant was delivered at 37 weeks' gestation to a 34-year-old gravida 1, para 0 woman with morbid obesity, chronic hepatitis B, and chronic hypertension. The woman's prenatal course was benign and she was negative for group B *Streptococcus*. She was brought to the hospital because of spontaneous rupture of membranes and some irregular contractions. The obstetrician decided to ripen her cervix with misoprostol, followed by an induction with oxytocin. Nine hours after the initiation of oxytocin, her cervix was fully dilated and she began pushing. The fetus was in the occiput posterior position and despite pushing, remained at -2 to -1 station. With each push, a late deceleration appeared. The fetal heart tracings changed from category 1 to category 2. Tracings progressed to fetal tachycardia, lack of accelerations, minimal moderate variability, and late and variable decelerations. *The plaintiff obstetrician was critical of the management. He pointed out that the combination of 1) the fetus being remote from a safe vaginal delivery, 2) the lack of descent despite the pushing, and 3) the fetal intolerance to labor, was an indication for a cesarean delivery.* Forceps were attempted 3 times. *The plaintiff obstetrician was critical of the use of forceps, stating that the intolerance to labor and the high station mandated discontinuation of the oxytocin and the need for an emergent cesarean section.* When the forceps failed, the obstetrician called for a cesarean delivery. The labor and delivery nurse informed the obstetrician that it could not be performed for 1 to 2 hours because of staffing issues. *The plaintiff obstetrician was critical of the unavailability of an emergent cesarean delivery at the hospital. The defense obstetrician said that this delay did not affect the fetus in an adverse way.* The woman's temperature became elevated during this period, and she was given ampicillin, gentamicin, and clindamycin for a presumed chorioamnionitis. At this point, her membranes had been ruptured for 36 hours.

The male infant was delivered through foul-smelling meconium-stained fluid. He was floppy without respiratory effort and covered in meconium. The arterial cord gas showed a pH of 7.14,  $\text{PCO}_2$  of 52 mm Hg (7.3 kPa),  $\text{PO}_2$  of 35 mm Hg (4.7 kPa), and base deficit of 10.9; the venous cord gas showed a pH of 7.04,  $\text{PCO}_2$  of 72 mm Hg (9.6 kPa),  $\text{PO}_2$  of 41 mm Hg (5.4 kPa), and base deficit of 11.7. *The plaintiff neonatologist pointed out that the gases were labeled incorrectly.* The placenta was unremarkable on gross and microscopic examination.

The infant underwent intubation to clear meconium, but none was found below the cords and the endotracheal tube was initially removed. Because the infant was apneic, positive pressure ventilation was provided by mask and bag. At 7 minutes of age, he underwent intubation secondary to persistent apnea and

**AUTHOR DISCLOSURE** Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

required 100% inspired oxygen to maintain saturations between 80% and 85%. The infant's Apgar scores were 2, 4, and 4 at 1, 5, and 10 minutes, respectively. At 14 minutes of age, the infant was admitted to the NICU where the heart rate was found to be 165 beats/min and the blood pressure was 32/18 mm Hg. His first arterial blood gas showed a pH of 7.16,  $P_{CO_2}$  of 9 mm Hg (1.2 kPa),  $P_{O_2}$  of 167 mm Hg (22.2 kPa), and a base deficit of 22.8. The neonatal team placed umbilical catheters. The infant's blood pressure continued to decline over the next several hours. Bicarbonate was provided and intravenous dopamine was started. The infant's complete blood cell count showed a white blood cell count of  $25,900/\mu\text{L}$  ( $25.9 \times 10^9/\text{L}$ ), hematocrit of 32.7%, and platelet count of  $106 \times 10^3/\mu\text{L}$  ( $106 \times 10^9/\text{L}$ ). Coagulation studies were very abnormal, with an elevated prothrombin time and partial thromboplastin time, an international normalized ratio greater than 10, and fibrinogen level less than 60 mg/dL ( $1.7 \mu\text{mol/L}$ ). Five hours after admission to the NICU, the infant received a transfusion of packed red blood cells followed by blood products to treat the disseminated intravascular coagulopathy. Before the transfusion was given, the infant's hematocrit dropped to 22%.

A complete physical examination was performed, which showed the infant to have a birthweight of 3,765 g (>90%), a head circumference of 38 cm (>90%), and a length of 55 cm (>90%). He was obtunded, had a large cephalohematoma with a boggy scalp consistent with a subgaleal hemorrhage, scalp bruising, and several head lacerations from the forceps. He also had left ear microtia without a visible canal, facial asymmetry, and a lesion in the inferior temporal quadrant of the left eye, identified subsequently as a corneal limbal dermoid. Head cooling was performed because the infant might have had criteria for therapeutic hypothermia.

Three days after birth, the infant developed seizures, which were controlled with phenobarbital and levetiracetam. On day 4, computed tomography was performed, which showed an extensive depressed left parietal skull fracture; subdural hematomas that extended into the interhemispheric fissure, around the cerebellar lobes, and tentorium, as well as around the cerebellar hemispheres; subarachnoid, parenchymal, and small intraventricular hemorrhages; and areas of low density and poor gray-white coloring, suggesting ischemia and infarction. The infant developed renal failure with a creatinine peak of 5.4 mg/dL ( $477 \mu\text{mol/L}$ ); the infant's renal function recovered clinically. The infant's liver enzymes were elevated to 3 to 4 times that of normal,

but also recovered. Extubation attempts failed twice, but were eventually successful. He was discharged breathing in room air and orally feeding. A genetics consultation identified the infant as having oculo-auricular-vertebral syndrome (ie, Goldenhar syndrome). Cardiac and kidney ultrasonography showed no anomalies, though the kidneys were echogenic secondary to the hypoxic-ischemic-anemic insult.

At 4 years of age, the child had significant growth delay and profound developmental delays as well as dysphagia, unilateral hearing loss, and visual deficits. The obstetrician and hospital were sued because of the below-standard-of-care management during labor and delivery. *The defendant experts maintained that the child's developmental delays were entirely secondary to Goldenhar syndrome. The plaintiff experts said that only the unilateral hearing deficit, visual acuity loss, and dysphagia were secondary to a genetic cause and that developmental delays were uncommon in Goldenhar syndrome, especially as severe as this child exhibited. Furthermore, the neonatal course is unremarkable in patients with Goldenhar syndrome, unlike this case where the infant was obtunded with intracranial hemorrhages, a skull fracture, and cerebral infarction, as well as anemia and renal failure.* The defendants settled before the trial.

## DISCUSSION

Goldenhar syndrome, also called oculo-auriculo-vertebral spectrum and craniofacial microsomia, is a congenital condition that involves malformations of the head, eyes, ears, facial bones, mouth and vertebrae. The acronym OMENS for orbit, mandible, ear, facial nerve, soft tissue is often used. Orbital distortion is typically present, as is mandibular hypoplasia. Ear anomalies include microtia, accessory preauricular tags and/or pits, and middle ear defects with hearing impairment. In 85% to 90% of cases, the defects of the ear are unilateral with the right side predominating. Renal, pulmonary, gastrointestinal, cardiac, and central nervous system deformities are uncommon.

The cause of Goldenhar syndrome is unknown; it is sporadically acquired secondary to a defect in development of the first and second branchial arches, and is thought to be secondary to a vascular insult. The incidence is 1 in 5,500 live births. Males are affected more frequently than females. Clinical presentations vary from mild to severe and the diagnosis can be made based on at least 2 features: microtia and facial asymmetry.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the evolution of neurodevelopmental impairments during development and the difference between transient and permanent impairments in NICU graduates (eg, developmental delay vs intellectual disability; tone abnormalities vs cerebral palsy).

## Suggested Readings

Acharya K, Baset D, Segall H, et al. Term newborn with unilateral craniofacial defects. *NeoReviews*. 2016;17:e184–e187

Birgfeld CB, Luquetti DV, Gougoutas AJ, et al. A phenotypic assessment tool for craniofacial microsomia. *Plast Reconstr Surg*. 2011;127(1):313–320

## Legal Briefs: Was the Adverse Outcome from Goldenhar Syndrome or Hypoxic-Ischemic Events?

Maureen E. Sims

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## Bilateral Lacrimal Sac Swelling in a Newborn

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### THE CASE

A term male newborn develops a painful bilateral swelling over both lacrimal sacs with purulent ocular discharge.

### PRENATAL, BIRTH, AND FAMILY HISTORIES

- Born to a 31-year-old gravida 3, para 2 woman at 39 weeks' gestation via elective cesarean delivery.
- Nonconsanguineous spontaneous conception.
- Normal prenatal maternal laboratory screening and fetal survey.
- Apgar scores: 10 and 10 at 1 and 5 minutes, respectively. No resuscitation was required.
- Birthweight: 3,925 g (90th percentile); length: 50 cm (50th percentile); head circumference: 34 cm (10th–50th percentile).

### PRESENTATION (DAY 5)

A 5-day-old male newborn presents to the emergency department with bilateral mucopurulent ocular discharge and is given a topical antibiotic. On the following day, he develops a painful bilateral swelling over both lacrimal sacs. No fever, nasal obstruction, or respiratory difficulty are present.

According to the mother, he had a blueish coloration of both medial canthal regions since birth.

### PROGRESSION

#### Physical Examination

- General: Active
- Head: Normocephalic; anterior fontanelle open and flat; bilateral tumefaction of around 1.5 cm of both medial canthi over the lacrimal sac area with marked edema and erythema of the overlying skin and presence of mucopurulent material; elastic left supraciliary nodule; patent nares; intact palate (Figs 1 and 2)
- Lungs: Regular rate and rhythm, breath sounds bilaterally equal
- Cardiovascular: S1 and S2 normal, no murmur; femoral pulses well felt; capillary refill 2 seconds
- Abdomen: Not distended; no hepatosplenomegaly
- Genitourinary: Normal term male genitalia; patent anus
- Skeletal: Equal movement of arms and legs, no visible abnormalities

**AUTHOR DISCLOSURE** Drs Constante, Rebelo, Bicho, and Fortunato have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





**Figure 1.** Normocephalic appearance of the neonate in the case, with anterior fontanelle open and flat.

### Laboratory Studies

Findings of biochemical and hematologic investigations were normal. Blood and ocular exudate cultures were both negative.

### Differential Diagnosis

- Bilateral dacryocystocele with bilateral acute dacryocystitis
- Bilateral dermoid cysts
- Bilateral nasal gliomas



**Figure 2.** Bilateral tumefaction of both medial canthi over the lacrimal sac area with marked edema and erythema of the overlying skin and presence of mucopurulent material.

### Actual Diagnosis

- Acute bilateral dacryocystitis due to bilateral dacryocystocele

### MANAGEMENT

The infant was admitted to the hospital and an ophthalmologist consulted. The medical team opted for conservative treatment, consisting of intravenous ampicillin and gentamicin for 10 days and topical gentamicin for 7 days. Both swellings and erythema subsided within 48 hours after receiving antibiotics (Fig 3).

After resolution of the acute symptoms, no further evidence was seen of nasolacrimal duct (NLD) obstruction or dacryocystocele.

### WHAT THE EXPERTS SAY

Congenital dacryocystoceles (sometimes also called dacryoceles, mucoceles, nasolacrimal duct cysts, or amniotocoeles) are relatively rare variants of NLD obstruction, accounting for only 0.1% of infants with congenital NLD obstruction, with approximately 25% having bilateral lesions. (1)(2)

They are produced when both the proximal and distal portions of the nasolacrimal system are obstructed—the distal obstruction is usually at the level of the membrane of Hasner and the proximal obstruction typically occurs in the common canaliculus or at the valve of Rosenmuller. Dacryocystoceles typically present in the neonatal period, initially as a firm subcutaneous bluish mass over the lacrimal sac area. (1)

The diagnosis is usually made clinically and further evaluation is generally not necessary, though neuroimaging can confirm the diagnosis. The lesions may resolve



**Figure 3.** Within 48 hours after receiving antibiotics, the swelling and erythema subsided.

spontaneously, but they frequently become infected and progress rapidly to acute dacryocystitis. (1)(2)

Acute dacryocystitis is an infection of the nasolacrimal system characterized by erythema, edema, warmth, and tenderness of the lacrimal sac, specifically just below the anatomic boundary of the medial canthal ligament, which may be accompanied by purulent discharge. It is a rare complication of isolated congenital NLD obstruction but occurs commonly with dacryocystoceles in 20% to 75% of the cases. However, the incidence of acute dacryocystitis shortly after birth is extremely rare, in that only a few cases have been reported in the world, especially bilateral cases. (3)

The presence of an enlarged erythematous mass overlying the lacrimal sac in a newborn is usually adequate to establish the diagnosis of an infected dacryocystocele. However, one must take into consideration some of the differential diagnoses, such as congenital and infantile hemangiomas, nasal gliomas, encephaloceles, and rarely, dermoid cysts. (2)(3)(4)

Bacterial cultures from the purulent discharge are commonly performed. These culture specimens can be obtained from the regurgitated sac contents. The microbiology of pediatric acute dacryocystitis is still not well studied, but the organisms most commonly isolated include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. (3)(5) Blood cultures and rarely lumbar punctures are suitable if there are signs of sepsis or if the treating physician and the emergency physician consider the patient at high risk for systemic infection. Imaging studies such as ultrasonography and CT scans have been reported but are not routinely advised. (3)

Acute dacryocystitis is a medical emergency in a newborn infant, and it must be treated promptly with systemic antibiotics to prevent the development of secondary preseptal or orbital cellulitis, meningitis, or brain abscess. Close monitoring should be undertaken because of the high risk for sepsis. (3)(4)

There is still no consensus regarding surgical treatment of an infected dacryocystocele. Probing is the surgical intervention of choice, but very few studies have specifically studied its efficacy and safety in children. Although successful NLD probing with no complications has been reported, systemic spreading of the infection has been reported as well. Nevertheless, some authors have also presented good results using a purely conservative approach. The final therapeutic decision should be made by a multidisciplinary team consisting of a pediatrician and/or neonatologist, an

ophthalmologist, and sometimes an otorhinolaryngologist. (3)(4)(5)

## CONCLUSIONS

- The diagnosis of congenital nasolacrimal duct obstruction is typically made based on history and physical examination alone and therefore pediatricians must be aware of this pathology.
- Congenital nasolacrimal duct obstruction may be complicated by acute dacryocystitis, which is a serious infection that warrants careful evaluation, immediate treatment, and close monitoring.
- The therapeutic decision in acute dacryocystitis, especially in newborns, is complex and should be made by a multidisciplinary team, always including broad-spectrum antibiotics.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the normal anatomy and ophthalmologic findings of the developing eye.
- Know the causes and clinical and laboratory features of acute neonatal infections of the eyes, including ophthalmia neonatorum.
- Know the management and complications of acute neonatal infections of the eyes, including ophthalmia neonatorum.

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## Toward More Effective Neonatal Resuscitation: Assessing and Improving Clinical Skills

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### Education Gaps

1. Pediatricians and neonatologists are responsible for teaching neonatal resuscitation skills to trainees, and therefore need to be aware of proven training techniques that objectively improve these skills.
2. Formal, structured newborn resuscitation training programs are becoming more widespread globally and represent an increasing financial and human resource investment. It is important that clinicians understand the advantages, effectiveness, and limitations of these programs, particularly in low- and middle-income settings.
3. There is a wide variety of techniques that can be used to teach resuscitation skills, including simulation, feedback devices, team training, video debriefing, and booster programs but evidence of their effectiveness is limited.

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#### ABBREVIATIONS

ENC	early newborn care
NLS	newborn life support
NRP	Neonatal Resuscitation Program
PPV	positive pressure ventilation
RCT	randomized controlled trial
SIB	self-inflating bag

### Abstract

Newborn deaths following birth asphyxia remain a significant global problem, and effective resuscitation by well-trained professionals may reduce mortality and morbidity. Clinicians are often responsible for teaching newborn resuscitation to trainees. Multiple educational methods are used to teach these skills, but data supporting their efficacy are limited. Mask ventilation and chest compressions are considered the basics of resuscitation. These technical motor skills are critically important but difficult to teach and often not objectively assessed. Teaching more advanced skills such as neonatal intubation is challenging, because teaching opportunities and working hours of learners have declined. Videolaryngoscopy appears to be an effective teaching tool that allows instruction during clinical practice. There is also emerging recognition that effective resuscitation requires more than individual clinical skills. The importance of teamwork and leadership is now recognized, and teamwork training should be incorporated because it

improves these nontechnical skills. Simulation training has become increasingly popular as a method of teaching both technical and nontechnical skills. However, there are unanswered questions about the validity, fidelity, and content of simulation. Formal resuscitation programs usually incorporate a mixture of teaching modalities and appear to reduce neonatal mortality and morbidity in low- and middle-income countries. Emerging teaching techniques such as tele-education, video debriefing, and high-frequency training warrant further investigation.

## Objectives After completing this article, readers should be able to:

1. Identify evidence-based methods to teach neonatal resuscitation skills.
2. Describe the role and limitations of structured formal neonatal resuscitation programs, and approaches to limit loss of skills over time.
3. Recognize the role of emerging educational approaches, such as simulation, self-directed learning, telemedicine, and video-assisted review.

## INTRODUCTION

The World Health Organization estimates that 700,000 newborns die from birth asphyxia each year. (1) Although millennium development goals have led to a reduction of global childhood illnesses, newborn mortality rates are slow to improve. This highlights the complexities of delivering effective newborn care, particularly resuscitation. Neonatal deaths can occur quickly and to prevent this outcome, there needs to be a rapid, appropriate response from well-trained staff, with suitable equipment. Effective newborn resuscitation offers an opportunity to substantially reduce mortality and morbidity. (2)

Despite advances in resuscitation techniques, translation into improved clinical practice is challenging. Neonatal resuscitation skills are often poor, (3) and training interventions are resource intensive and specialized. The International Liaison Committee on Resuscitation has stated that there is a need for careful assessment of newborn resuscitation training. This includes determining 1) which training interventions effectively teach skills, 2) how often teaching should occur, and 3) how educational outcomes should be measured. (4)

The aim of this review is to evaluate methods designed to effectively teach newborn resuscitation skills. We performed a systematic search of 5 databases: Medline, Embase, CINAHL, Academic Search Complete, and Cochrane. The following medical subject headings and search terms were used: ([newborn OR neonatal OR infant] AND resuscitation AND [train\* OR teach\* or NRP OR NLS OR simulation]).

We limited our results to randomized studies and meta-analyses of newborn resuscitation training interventions.

## SKILLS TRAINING

### Positive Pressure Ventilation

Pulmonary aeration is required for successful transition to extrauterine life. Approximately 3% of newborns fail to establish spontaneous respirations during this transition. International guidelines recommend that these infants receive positive pressure ventilation (PPV) within 1 minute of birth. (4) PPV is the cornerstone of successful resuscitation and is usually administered via a facemask. Effective facemask ventilation is technically challenging and difficult to learn. (3) In fact, trainees perform better at advanced interventions than basic skills such as administering PPV. (5) Several studies have investigated how best to teach this critical, lifesaving technique.

Wood et al compared mask holds used when delivering PPV, and assessed the impact of written instructions and demonstration. (6) Clinicians were randomly allocated to use 2 different masks with 1 of 3 holds: 2-point hold (Fig 1A), OK rim hold (Fig 1B), and stem hold (Fig 1C). The optimal hold was different for each mask. As shown in Fig 2A, the 2-point top hold was best for the Laerdal facemask (Laerdal Silicone facemask, Laerdal, Stavanger, Norway) and, as shown in Fig 2B, the OK rim hold was best for the Fischer and Paykel mask (Fisher & Paykel Healthcare, Auckland,



Figure 1. Mask holds, all with a Laerdal mask. A. Two-point top hold. B. OK rim hold. C. Stem hold.

New Zealand). The method of teaching also appears to be important. Written instruction alone was relatively ineffective and reduced leak by only 8.8%. However, written instruction combined with a teaching demonstration reduced leak by 24%. The number and variety of available masks have increased since this study and highlights the challenge of teaching optimal holds for each mask. The introduction of a new mask should be preceded by an evaluation of the best method to apply that mask followed by specific instruction in the optimal hold.

PPV is commonly delivered via a self-inflating bag (SIB) or a T-piece device. (7) Mathai et al randomized 100 participants in a newborn resuscitation program in India, to a demonstration of the use of a T-piece or a SIB. (8) Participants were then assessed performing PPV with the assigned device using a skill check monitor (Laerdal Health). The researchers found that while participants scored more poorly in the equipment setup phase (longer duration), they scored higher in providing a good seal and giving adequate pressure with less need for corrective action when the T-piece was used. This indicates that after a simple demonstration of PPV devices, clinicians take longer to set up the T-piece, but the PPV administered is more effective than with the

SIB. This suggests that careful attention should be given to teaching and assessing correct setup of the T-piece. The learners reported satisfaction with both devices.

### Intubation

Fewer neonates undergo intubation in the modern era and fewer trainees are rotating in intensive care units, therefore, the opportunities for teaching neonatal intubation have decreased. There has been an interest in alternative methods and adjuncts to help teach neonatal intubation. Teaching packages have included mannequins, (9) animal models, (10) cadaveric specimens, smartphone applications, (11) and clinical intubation practice with advanced equipment. (12)

Andreatta et al published 2 quasi-randomized controlled trials (RCTs) comparing animal models to mannequins for intubation training. (10)(13) The intubation success rate and observed skills were similar after each intervention. Although feasible in the authors' setting, the ethical implications, cost, and difficulty accessing animal models makes widespread applicability unlikely.

Intubation models are readily available for teaching intubation. However, most are of low fidelity and imaging has shown that neonatal mannequin airway dimensions differ substantially from those of a neonate. (14)

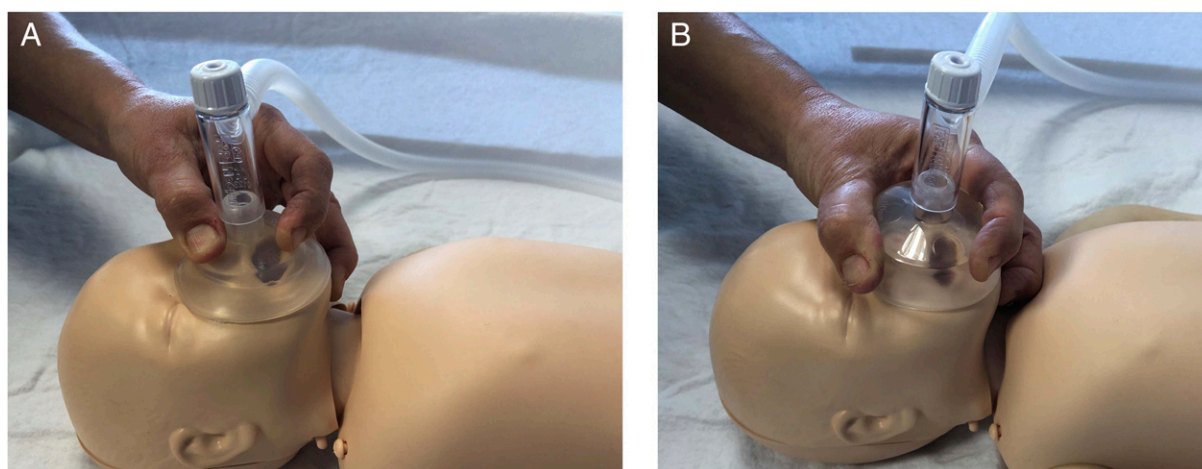


Figure 2. Optimal mask holds. A. Laerdal mask 2-point top hold. B. Fisher & Paykel OK rim hold.



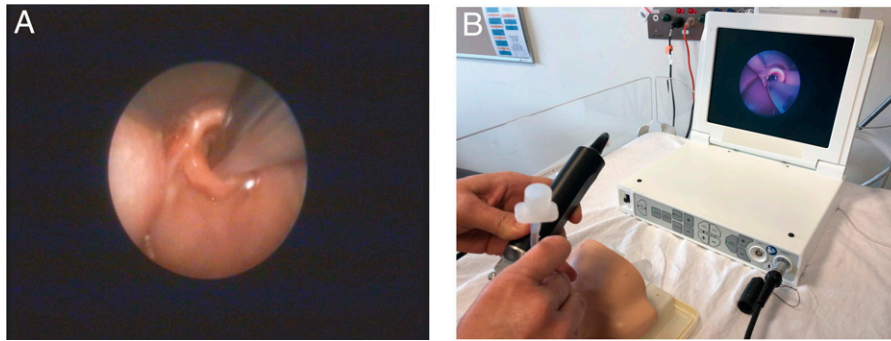


Figure 3. A. Videolaryngoscope screen during intubation. B. Videolaryngoscope-assisted mannequin intubation.

Adjuncts that aid teaching in the clinical setting therefore warrant investigation. Videolaryngoscopes allow the instructor to share the learner's view of the airway, thereby allowing the instructor to more accurately guide the learner (Fig 3). O'Shea et al demonstrated that when instructors were able to view the videolaryngoscope screen, the success rate of first intubation attempts by learners increased from 42% to 66%. (12) A recently updated Cochrane systematic review included 3 RCTs investigating videolaryngoscopy for teaching newborn intubation. (15) Compared with conventional laryngoscopy, the time for successful intubation, frequency of adverse events, and number of intubation attempts were similar. However, the success rate at first attempt was increased when the videolaryngoscope was used.

### Chest Compressions

The important elements of chest compression technique include hand position, compression depth, chest recoil, and timing of compressions. Huynh et al compared 2-thumb to 2-finger compression in a randomized, crossover study in a mannequin model. (16) They found that the 2-thumb technique (Fig 4) resulted in improved compression depth, reduced variability in depth, and less decay over time. A



Figure 4. Chest compression: 2-thumb technique.

recent randomized crossover mannequin study compared 3 groups: 1) a new 2-thumb technique, 2) the currently commonly used thumb technique, and 3) the commonly used 2-finger technique. (17) The new technique (Fig 5) "consists in directing 2 thumbs at the angle of 90 to the chest while closing the fingers of both hands in a fist." (17) While the 2-finger technique demonstrated improved chest recoil, both thumb techniques displayed greater compression depth. The new thumb technique was not superior to the commonly used thumb technique when compression depth was compared.

Metronomes acting as auditory prompts may aid teaching of correct timing of chest compressions. A chest compression feedback device consisting of a metronome combined with pressure data feedback ("Rhythm of Life Aid") has been investigated in a mannequin RCT. (18) This device led to less variability in rhythm and pressure applied during chest compressions when used during simulated chest compressions. However, real-world performance after training with the device has not been assessed.

### Team Training

The importance of human factors in the management of medical emergencies is becoming increasingly recognized. Several RCTs have focused on the impact of team training techniques on newborn resuscitation skills. (19)(20)(21) The learning objectives of team training are to recognize the underlying causes of errors made during neonatal resuscitation and to improve team behaviors. Education around team functioning is heterogeneous but typically includes the frequency, causes, and description of human error in newborn resuscitation; the identification of team behaviors that reduce error; and specific communication behaviors that improve effectiveness.

The use of standardized communication compared with nonstandard communication has been investigated. (22) Casual terms such as "it's good," "oh, really juicy," or "she needs blood" were replaced by standard terms such as "heart rate above 100" or "breath sounds decreased left."



Figure 5. Chest compression: new thumb technique.

Standardized communication did not improve simulation skills. However, a trend toward decreased error rate and shorter time to initiation of PPV and chest compressions was observed in the standardized communication group. Given the extremely small sample size ( $N=13$ ), the study was underpowered to detect a statistically significant difference. Further research of the impact of standardized communication is warranted.

Anesthesiologists have developed standardized approaches to team training. However, an RCT evaluating crisis resource management and anesthesia nontechnical skills for newborn resuscitation training in 99 participants unexpectedly found that these approaches had no impact on teamwork skills. (19) Thomas et al have investigated the addition of teamwork training to the Neonatal Resuscitation Program (NRP) in 2 RCTs. (20)(21) In contrast to the anesthetic intervention, both studies found that this team training intervention improved teamwork behaviors, and 1 study showed a shorter duration of simulated resuscitation. (21) More frequent teamwork behaviors were also observed at a 6-month follow-up. The quality of evidence was reduced by the high attrition rates in this study, and only one-third of participants were followed up. (21) These results suggest that team training models designed for adult anesthetic practice may not be readily transferrable to neonatal resuscitation, without modification.

## EDUCATIONAL METHODS

### Simulation

Simulation describes an educational approach in which a real object, state, or process is imitated for the practice of problem solving, skills, or judgment. (23) Studies of the efficacy of simulation in newborn resuscitation training have compared simulation to no simulation or other

methods, high- versus low-fidelity simulation, and mannequin death in simulation.

Four RCTs compared newborn resuscitation simulation to self-directed study, lectures, no training, or other training. (24)(25)(26)(27) Cavaleiro et al observed no difference in knowledge acquisition among 45 medical students randomized to a 30-minute simulated training session compared with 30 minutes of self-directed study. (24) Bruno et al randomized 33 obstetric residents to simulation or lecture-based newborn resuscitation training. (25) There was a greater improvement in knowledge and confidence in the simulation group. However, performance was equal at 6 months in both groups. In a large cluster RCT, Rubio-Gurung et al randomized 240 staff members at 12 hospitals to 4 hourly in-situ simulation training compared with no simulation training. (26) In-situ simulation refers to simulation performed in the learner's own working environment. The control group had only received the standard hospital resuscitation training. Superior team and clinical skills were found in staff after in-situ simulation compared with no training. Lee et al found that 27 emergency department residents randomized to a newborn resuscitation simulation course displayed improved knowledge, confidence, and clinical skills compared to an emergency medical training course. (27) Taken together, this evidence suggests that simulation teaching results in greater knowledge and confidence than other methods. However, its efficacy in novice practitioners such as medical students has not been established. In-situ simulation training has been supported by the largest RCT, by Rubio-Gurung et al. (26)

Criticisms of simulation sometimes focus on a lack of realism. Therefore, more realistic or higher-fidelity simulation may improve the training environment. Five trials have compared low- with high-fidelity newborn resuscitation simulation. (21)(28)(29)(30)(31) Learner satisfaction and confidence were greater with the use of high-fidelity simulation in all 5 studies. However, 3 studies, Campbell et al ( $N=15$ ), Curran et al ( $N=66$ ), and Nimbalkar et al ( $N=101$ ) found no difference in teamwork or clinical skills between high- and low-fidelity newborn resuscitation simulation. (28)(29)(30) Although it is postulated that high-fidelity simulation may increase realism and therefore mimic real-life stress, Finan et al detected no difference in subjective stress or buccal cortisol levels among 16 neonatal fellows randomized to low- or high-fidelity simulation. (31) Thomas et al randomized 98 interns to receive high fidelity in addition to team training, low fidelity plus team training, or low fidelity without team training. (21) All 3 groups received the extra training in conjunction with the standard NRP training. (21) In contrast to the previously



mentioned studies, Thomas et al found that the high-fidelity group displayed more teamwork behaviors and completed resuscitations in a shorter time than the group that received low fidelity without team training.

Lizotte et al investigated death during simulation compared with survival during simulated resuscitation in 42 pediatric residents. (5) Participants undertook a simulation of an infant born without a pulse. They were randomized to a scenario in which the mannequin responded to appropriate interventions and survived or the mannequin failed to respond to appropriate interventions and died. There was no difference in skills, reported stress, or performance between the groups. The authors noted that any training increased salivary cortisol and this increase was no different between groups exposed to death versus those exposed to survival.

These studies indicate that there is some evidence that simulation training for newborn resuscitation improves knowledge, clinical skills, team behaviors, and confidence in clinicians and hospital staff. High-fidelity simulation appears to be associated with greater confidence and satisfaction but does not seem to improve clinical skills. Interns displayed improved teamwork and clinical skills with high-fidelity simulation, but this has not been found in other learners. Interestingly, death during simulation may be useful for improving fidelity, preparing practitioners for this outcome, and teaching ethical practice. Any simulation training causes significant stress to learners and it is vital that this is considered and managed by trainers.

### Formal Training Courses

Formal newborn resuscitation programs, based on internationally agreed-upon recommendations, (4) have been developed to standardize resuscitation training. These include the NRP, (7) Helping Babies Breathe, (32) Newborn Life Support (NLS), (33) and the Australian NeoResus program. (34)

In a randomized study, Dunn et al found that a 1-day educational course on newborn resuscitation increased participant knowledge and skills compared with clinicians who did not participate in a course. (35) Training included a didactic element and clinical skills were taught via demonstration, practice, and testing.

Five trials have examined newborn resuscitation training in low- and middle-income countries. (36)(37)(38)(39)(40) The resuscitation training was sometimes incorporated as part of a package of newborn care, and the standard programs were usually modified for a low-resource setting (eg, excluded teaching about chest compressions, intubation, and medications). Opiyo et al (N=83 staff) found that the quality of newborn resuscitation practice was higher in nurses and midwives in Kenya randomized to NLS training,

compared with no training. (36) The quality of practice was defined as the proportion of observed, appropriate, first steps of resuscitation. Xu et al (N=184 staff), in a large cluster randomized trial in 22 hospitals in China, showed that a quality improvement intervention that included neonatal resuscitation training, the establishment of hospital guidelines, and the formation of emergency teams, led to improved trainee knowledge and decreased the proportion of infants with 1-minute Apgar scores less than or equal to 7. (38) In a cluster RCT, Gill et al randomized traditional birth attendants in Zambia (N=127) to 2 groups, with 1 group exposed to a modified NRP training program with a sepsis management algorithm while the other group continued its existing practice with basic obstetric skills and the use of clean delivery kits. The intervention training package reduced early neonatal mortality (up to day 28 after birth) by 45% (rate ratio 0.55, 95% CI 0.33 to 0.90) in 3,559 births attended during the study period. (37) In 2 cluster RCTs conducted in low-income countries (Argentina, Congo, Guatemala, India, Pakistan, and Zambia), Carlo et al investigated an early newborn care (ENC) approach combined with a modified NRP and an NRP refresher at 6 months compared with ENC alone. (39)(40) Neonatal mortality was measured at 7 days and physicians, nurses, midwives, and traditional birth attendants were educated using a train-the-trainer model. In one study, Carlo et al (39) included 62,366 term infants and in the other study, they included 1,096 preterm infants born during the study periods. (40) Both studies found that NRP training did not reduce neonatal mortality (at 7 days), stillbirth, or perinatal death in term or preterm infants. One study found a relative risk of 0.87 (0.65 to 1.16) (39) and the second study reported a relative risk of 1.03 (0.83 to 1.27). (40) Heterogeneity of the participants may explain the discrepancy in results among all 5 trials. Gill et al included only traditional birth attendants, whereas both studies by Carlo et al included traditional birth attendants, physicians, nurses, and midwives. A recent Cochrane systematic review (41) pooled analyses from the 3 community-based RCTs (37)(39)(40) and found that standard formal newborn resuscitation courses reduced early neonatal mortality with a relative risk of 0.88 (0.78–1.0). Of note, all relevant studies were in low-income countries and the greatest impact was on training traditional birth attendants.

### EMERGING APPROACHES

Emerging educational interventions include modifications to existing standard courses such as tele-education, self-

directed practice and cognitive aids, and interventions designed to address loss of skills over time.

### Tele-education

Resuscitation training courses consume significant resources, and staff and clinicians who practice in regions remote from training centers may be unable to participate in trainings. To address these barriers, Jain et al examined the benefit of tele-education. (42) They randomized 48 nurses to receive NRP via tele-education or face-to-face education in India. (42) They found no difference in knowledge, skills, or satisfaction, suggesting that tele-education is a reasonable alternative to face-to-face classroom teaching.

### Self-Directed Practice

Self-directed practice offers learners flexibility, control over the pace of new information, and benefits of using repetition. (43) This approach may also improve the educational efficiency of training programs, allowing time for simulation, deliberate practice, and synthesis of information. Meaney et al compared self-directed learning with instructor-led teaching in Botswana. (44) There was no difference in simulation performance between methods, and both groups demonstrated improved clinical skills. Weiner et al randomized 46 novice clinicians to self-directed education or to a traditional class of lectures and skill stations. (43) Self-directed education provided an instructional video, textbook, simulation kit, and 90-minute simulation session. There was no difference in knowledge, simulation performance, satisfaction, or confidence between groups. Similarly, Cavaleiro et al found no difference in knowledge between medical students randomized to a 30-minute simulated neonatal resuscitation compared with 30 minutes of self-study. (24) While self-directed learning has not been shown to be superior to standard models, these studies suggest that it is not inferior. Given the advantages in terms of educational efficiency, adoption of self-directed practice may allow for the incorporation of additional teaching tools such as simulation or video-assisted debriefing into teaching programs.

### Cognitive Aids

Cognitive aids have been proposed as methods to guide decision making and teach neonatal resuscitation. Several methods have been investigated in newborn resuscitation including algorithm display, audiovisual prompts and feedback, and a smart phone application. Bould et al randomized 32 anesthesia residents to a visible cognitive aid (NRP algorithm poster) during simulation compared with no aid. The visual aid did not improve performance. (45) Fuerch et al

randomized practitioners to the use of a decision support tool (NeoCue) during simulation. (46) This tool consisted of visual and auditory prompts to commence stages of resuscitation and a metronome. The use of the tool during a simulation resulted in improved performance. Lund et al investigated a smart phone intervention in a cluster randomized trial in Ethiopia. (47) The application consisted of a package of obstetric and neonatal interventions including neonatal resuscitation. The authors found that while knowledge and skills increased, there was no change in neonatal mortality.

### Booster Courses

From the earliest randomized trials on the impact of formal education courses, poor retention of skills after a single training intervention has been recognized as a major problem. Dunn et al found that although a newborn resuscitation course improved knowledge and skills, skills were not maintained at the 6-month follow-up. (35) To address this loss of skills and knowledge, various booster training programs have been investigated. (4) “Booster” or refresher programs refer to educational interventions designed to supplement the original training to improve retention of skills and knowledge. They consist of shorter interventions that supplement the original teaching such as a simulation session, video, or knowledge teaching.

Pediatric residents exposed to a booster simulation training session 7 to 9 months after initial NRP training displayed improved performance in simulation and teamwork skills at 15 to 18 months. (48) The booster consisted of a single simulation scenario and a performance debriefing afterwards. Kaczorowski et al randomized 44 family medicine residents to 3 arms after NRP training. (49) The first included a video booster and self-directed practice, the second consisted of a booster of an instructor-led 2-hour practice, and the third arm consisted of no booster. All boosters occurred 3 to 5 months after NRP and reassessment occurred 6 to 8 months after the NRP. At reassessment, knowledge and skills were reduced in all groups. There were fewer errors in skills in the instructor-led booster arm compared to the video or no booster groups. In the study by Carlo et al, clinicians in the intervention group attended an ENC program, an NRP, and a booster program after 6 months. (40) The contents of the booster are not well described. Those in the control group received the initial ENC alone. There was no difference in early neonatal mortality between those who received ENC, NRP, and the booster compared with ENC alone.

Clinical experience is an important confounder in these studies, particular when following up junior trainees at the

beginning and end of training periods. (25) However, there is some evidence that repeat or booster training is of benefit. Any booster (including self-directed learning, simulation, or instructor-led sessions) appears to be superior to none. Although basic resuscitation is a small part of the ENC package, it was not found to improve neonatal mortality. The optimal timing of booster training, the content, educational method, repeated training, and follow-up remain important questions with little evidence for guidance.

### Video Debriefing

Video debriefing consists of reviewing clinical resuscitations in a classroom setting and has been used to teach teamwork behaviors. Sawyer et al investigated the use of video-assisted debriefing in an RCT compared with an oral debriefing. (50) Despite the feasibility and user acceptability, there was no difference in clinical skills compared with controls.

### Selecting and Measuring Outcomes of Educational Interventions

Measuring objective, reproducible, clinically relevant outcomes of teaching interventions is essential to improve training methods. The outcomes measured in studies included in this review were diverse. The main domains assessed were knowledge, clinical skills, user experience, and clinical outcomes.

Knowledge was frequently assessed via pre- and post-test comparison. Validity and reliability threats to knowledge assessments were poorly addressed in studies. Validity threats included repeated testing and regression toward the mean. Reliability threats consisted of assessor training, test difficulty, or simplicity. Clinical skills in the described studies were measured by performance using mannequins, animal models, simulation, or during clinical practice. Skills stations, often mannequin-based, were observed in person or via video to introduce blinding. Clinical skills were also assessed through performance in simulation; however, the definition of desirable outcomes in simulation varied considerably. (28)

Studies often had poorly controlled confounders (such as facilitator coaching that occurred during simulation assessments). Use of checklists can be considered as they have been developed and reported to reduce interassessor variability and detection bias. Methods that objectively measure clinical skills such as respiratory function monitors (6) or modified mannequins (16) that measure compression depth (16) result in more objective and reproducible measurements.

There is also uncertainty whether training leads to improvements in the clinical setting. Evidence shows that

performance using mannequins does not necessarily translate into clinical performance. (9) Although important for acceptability of a program, reporting of participant satisfaction and confidence is vulnerable to bias and it is unclear whether these measures translate into improved performance in the clinical setting. Objective measurements of stress including buccal cortisol levels may be preferable. (5) (31)

Clinical outcomes in the studies analyzed in this review included observed births or resuscitations, neonatal morbidity, and mortality. Observed skills were vulnerable to detection bias and can be improved by the use of blinded assessors; an objective, validated checklist; or another objective measurement of skills. It is challenging to compare outcomes such as hypoxic-ischemic encephalopathy because studies used different definitions. Neonatal mortality is a critically important measure of training outcomes, particularly in middle- and low-income countries. However, it may be difficult to distinguish neonatal mortality from stillbirth in low-resource settings; therefore, perinatal mortality should also be considered. In these settings, neonatal resuscitation may be more effective as part of a package including obstetric care. Mortality is also unlikely to be a useful marker of training outcomes in high-income countries, and alternative measurement of clinical efficacy needs to be considered. None of the reviewed studies reported long-term neurodevelopmental follow-up.

### CONCLUSION

There is some evidence to guide clinicians tasked with teaching newborn resuscitation. Teachers should also be aware of emerging techniques that have been evaluated. Teaching effective ventilation techniques is vital and attention should be focused on correct mask hold. Chest compression training should consist of a thumb-based technique. Feedback mechanisms enhance the teaching of chest compressions. Although mannequins can be used to teach neonatal intubation, videolaryngoscopy is a more effective tool. Team training should be incorporated, though adult modules are not transferrable, and standardized neonatal resuscitation training needs to be developed and tested in randomized trials. Structured formal resuscitation training programs reduce neonatal mortality in low- and middle-income settings, but they are most effective for clinicians with minimal preexisting knowledge. Despite their significant costs, structured programs have not been shown to have clinical benefits in high-income countries. Simulation training appears to confer benefit. However, high-fidelity

simulation has not been shown to be consistently superior to low-fidelity simulation. Novel uses for simulation training such as death during simulation warrant further investigation. Loss of skills after training is a major problem. Any booster training is superior to none, but the optimal frequency and format of booster sessions are not yet known. Novel methodologies including video debriefing, self-directed learning, and tele-education are being developed and may offer alternatives to traditional approaches.

## EVIDENCE SUMMARY

- Structured formal neonatal resuscitation programs reduce neonatal mortality and morbidity based on data from 5 cluster RCTs with 66,162 participants; however, generalizability to high-income settings and all health-care staff is limited. (41)
- Videolaryngoscopy is superior to direct laryngoscopy for teaching neonatal intubation, based on 3 RCTs with 467 participants. (15)
- Based on minimal evidence as well as consensus, simulation training is effective for improving neonatal resuscitation clinical skills (24)(25)(26); however, high-fidelity simulation is not more effective than low-fidelity simulation. (21)(28)(29)(31)
- Based on minimal research evidence, booster training improves retention of clinical resuscitation skills. (40)(48)(49)
- Based on minimal research evidence, video debriefing, tele-education, and self-directed practice may be equivalent to traditional methods for teaching newborn resuscitation. (24)(42)(43)(44)(50)

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the proper approach to airway management in the delivery room.
- Know the indications for assisted ventilation, including continuous positive airway pressure, immediately after birth and how to assess its effectiveness.
- Understand how to use self-inflating and flow-inflating bags or T-piece resuscitators to provide assisted ventilation immediately after birth.
- Know the indications for, techniques, and potential complications of chest compression immediately after birth.

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**Educational Perspectives: Toward More Effective Neonatal Resuscitation:  
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# The Neonatal Microbiome and Metagenomics: What Do We Know and What Is the Future?

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## Education Gap

Clinicians caring for pregnant women and/or neonates should recognize the development of the neonatal microbiome, the impact of common maternal and neonatal interventions on this development, and the potential role for dysbiosis in the development of disease.

## Abstract

The human microbiota includes the trillions of microorganisms living in the human body whereas the human microbiome includes the genes and gene products of this microbiota. Bacteria were historically largely considered to be pathogens that inevitably led to human disease. However, because of advances in both cultivation-based methods and the advent of metagenomics, bacteria are now recognized to be largely beneficial commensal organisms and thus, key to normal and healthy human development. This relatively new area of medical research has elucidated insights into diseases such as inflammatory bowel disease and obesity, as well as metabolic and atopic disorders. However, much remains unknown about the complexity of microbe-microbe and microbe-host interactions. Future efforts aimed at answering key questions pertaining to the early establishment of the microbiome, alongside what defines its dysbiosis, will likely lead to long-term health and mitigation of disease. Here, we review the relevant literature pertaining to modulations in the perinatal and neonatal microbiome, the impact of environmental and maternal factors in shaping the neonatal microbiome, and future questions and directions in the exciting emerging arena of metagenomic medicine.

## Objectives After completing this article, readers should be able to:

1. Describe the nomenclature of commonly used terms related to the evaluation and measurement of the microbiome and its metagenomes.

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### ABBREVIATIONS

BMI	body mass index
DOHaD	Developmental Origins of Health and Disease
GBS	group B <i>Streptococcus</i>
HMO	human milk oligosaccharide
NEC	necrotizing enterocolitis
Next-Gen	Next-Generation
PPROM	preterm premature rupture of membranes
rRNA	ribosomal RNA
VLBW	very-low-birthweight
WGS	whole genome shotgun

2. Recognize the potential impact of exposures during pregnancy on the maternal microbiome and the development of the neonatal microbiome.
3. Discuss the influence of common interventions during the perinatal and neonatal period on the development of the neonatal and early infant microbiome.
4. Review the future directions and unanswered questions pertaining to the neonatal microbiome and its potential long-term effects on health and disease.

## INTRODUCTION

Historically, bacteria and microorganisms have largely been considered pathogens that drive infectious illness and disease. For example, Koch's postulates described in 1884 focused on the causative relationship between microbes and disease. However, we now know that microbes are generally commensal, and thus, far less likely to be "foes" and far more likely to be "friends." Notably, the first description of bacteria by Antony van Leeuwenhoek in 1683 demonstrated the symbiotic relationship of a community of bacteria living on human teeth. Moreover, the "hygiene hypothesis" states that a lack of exposure to microbes and bacteria early in life leads to higher rates of atopy and allergic diseases, such as eczema and asthma. Consistent with this belief that bacteria are less likely to be pathogens and more likely to be commensals, there is an evolving and new appreciation of resident microbes and their function within their human niches. This appreciation has resulted from significant and exponential advances in Next-Generation (Next-Gen) sequencing and computational analysis.

The developmental origins of health and disease (DOHaD) hypothesis, also known as the "fetal origin of adult disease" hypothesis, postulates that adverse in utero conditions contribute to adult-onset metabolic diseases. Early on, our laboratory and others postulated that the microbiome underscores and is a likely effector mechanism of the DOHaD. In the interval since, we and others have demonstrated exposures that modulate the microbiome and are associated with metabolic disease later in life. (1)(2)(3)(4)(5)(6) Others have shown that mice raised in germ-free (also known as "gnotobiotic") settings are susceptible to immune and metabolic disorders that cannot be ameliorated or restored unless the mice are exposed to bacteria during pregnancy and/or neonatal life. (7) Therefore, the initial development of the microbiome in the neonatal period represents a unique and critical time in which the

establishment and development of the microbiome occurs, with potential long-term implications to health and disease. As such, understanding how and when the microbiome is first established and what external factors modify its development is a key focus within the field of metagenomics.

Before delving further into the characterization and development of the microbiome in the neonate and infant, one must first have a clear understanding of the definitions of common terms used throughout this review.

### Dysbiosis

Abnormal distribution and/or quantity of bacterial species within a specific body site.

### Metagenomics

The study of microbes in their natural living environment and their respective genomic composition using non-culture-based methodology. The field of metagenomics is relatively new as a result of advanced technological means for evaluating the microbiome, bypassing previously used culture methods.

### Microbiota

Organisms present within a community, usually referring to an animal/human host.

### Microbiome

The total microbial community and their genomes, which include commensal as well as pathogenic organisms.

We will first review the techniques used to assess and characterize the microbiome before reviewing the characterization and changes in the microbiome during pregnancy and its relationship to preterm delivery. Next, we will review the development of the microbiome in the neonate and infant, focusing on its relationship to mode of delivery, maternal diet, infant feeding practices, and gestational age at birth. Then, we will explore common ailments

potentially associated with dysbiosis of the microbiome in the neonate, such as necrotizing enterocolitis (NEC). Finally, we will conclude with a discussion on the future aims and unanswered questions related to the field of metagenomics and the neonatal microbiome.

## METAGENOMIC SEQUENCING AND ANALYSIS AS A MEANS OF ASSESSING MICROBIOME COMMUNITY MEMBERS AND FUNCTION

### Detecting Bacteria Present in a Given Microbiome Niche Community

Determining which bacteria are present in any given microbiome community profile has proven challenging. Previously, culture-based methods were the primary means for bacterial taxonomic profiling, which limited the ability to detect fastidiously growing organisms or organisms that become nonviable during processing. Notably, as many as 60% to 85% of bacteria detected using metagenomic methodologies will not grow in standard bacterial culture media. (8)(9) Therefore, researchers have developed cultivation-independent techniques to evaluate the presence of bacteria by using genetic material and Next-Gen sequencing. Next-Gen sequencing, also known as high-throughput sequencing, allows for the quick sequencing of either DNA or RNA and has revolutionized the field of metagenomics. We will briefly review 2 main metagenomic sequencing methods currently used: 16S ribosomal RNA (rRNA) and whole genome shotgun (WGS) sequencing.

### 16S-Based Metagenomics

Universal amplicon sequencing of variable regions of the 16S rRNA allows for the taxonomic classification of bacteria because of its highly conserved regions among phylogeny. (10) Researchers are able to evaluate the phylogeny and taxonomy of bacteria through the 9 hypervariable regions (V1-V9) to allow for classification. However, there are significant limitations to 16S-based metagenomic approaches. Specifically, this method cannot always accurately differentiate between closely related species because of sequence homology, and genus-level taxonomy is generally considered the nearest reliable refined prediction, with species and strain generally far less reliable. (11) In addition, the use of certain variable regions may underestimate certain genera of bacteria and overestimate others. For example, the Human Microbiome Project Consortium found that V6V9 amplicons may underestimate *Bacteroides* but provide good coverage for the identification of *Pseudomonas* and *Escherichia*. (12)

### Whole Genome Shotgun

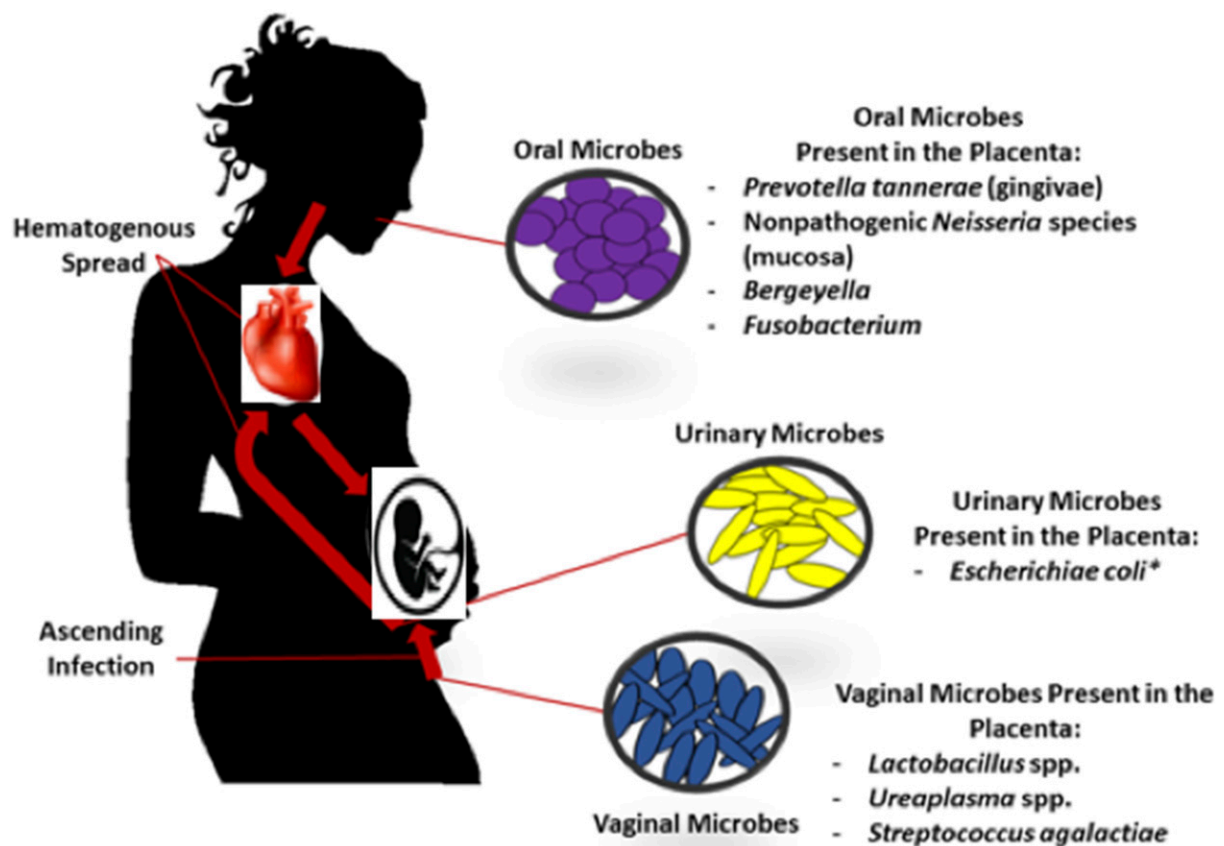
WGS sequencing allows researchers to evaluate more refined taxonomic classification to the species and strain level, with the added benefit of capturing the total gene content and metabolic capacity; this is termed “functional metagenomics.” (13)(14) However, because of the significantly higher amount of raw sequence data derived from WGS, it proves to be more costly and poses significant bioinformatics challenges. (15)

WGS generates thousands of sequence reads that are assembled into genomes and assigned taxonomy based on reference genomes. Although numerous organisms have reference genomes, many still do not, and therefore, de novo assembly of the microbial genomes without these reference genomes commonly occurs. This de novo process leads to potential distortion of species abundance or even generates chimeric genomes by splicing together genetic material of 2 different microorganisms into a single sequence. (16) However, the depth of evaluation with WGS can be deeper with the ability to examine function with genome assembly. While this is done with 16S data, function is inferred from the taxa present rather than the presence of the genes. (17)

Regardless of whether one pursues WGS or 16S sequencing, both can only describe the bacterial community structure and its potential for functional capabilities. Further tools can help evaluate dynamic gene expression patterns and study the collection of metabolites associated with the sampled microbiome through the use of metatranscriptomics and metabolomics, respectively. The integration of metagenomics, metatranscriptomics, and metabolomics presents its own unique challenges and is beyond the scope of this review.

## THE MICROBIOME DURING PREGNANCY AND ITS RELATIONSHIP TO PRETERM BIRTH

Preterm birth is the leading cause of neonatal morbidity and mortality throughout the world. However, little is understood about the etiology of preterm birth. Previously, many believed that an ascending infection from the vagina led to the development of preterm premature rupture of membranes (PPROM), which then ultimately led to preterm labor and birth. However, the ascending spread of bacteria to the placenta via the vagina is not the only route for placental bacterial colonization as seen by more recent evidence, which supports hematogenous spread of bacteria from the oral cavity (Fig 1). (18) Contrary to the belief that the placenta, amniotic fluid, and fetal tissues are “sterile,” with the advent of metagenomics, our laboratory and others have



**Figure 1.** The unique placental microbiome and the colonization of the placenta via hematogenous and/or ascending pathways. The placenta harbors a unique microbiome that includes bacteria from the vagina, urinary tract, oral cavity, and other regions of the body. Bacteria from the vaginal tract, such as *Streptococcus agalactiae*, are believed to spread to the uterus via an ascending route whereas bacteria from the urinary tract and oral cavity are believed to spread hematogenously to the placenta. These bacteria have also been found in the amniotic fluid, and the evidence is mounting that the womb is not actually sterile but serves as the first exposure to bacterial products to the fetus. \**Escherichia coli* has the highest abundance in the placenta, and is a common pathogen associated with urinary tract infections in pregnant women.

shown that the placenta harbors its own unique, low-biomass microbiome. (14) It is possible that dysbiosis of the placental microbiome contributes to preterm birth. However, what exactly is known to occur within the maternal microbiome during pregnancy, and how does it potentially relate to preterm birth?

#### Vaginal Microbiome and Associated Changes During Pregnancy

During pregnancy, the microbiome in the vagina is dynamic and changes based on the duration of pregnancy, the maternal diet, and maternal body mass index (BMI), among other factors. (19) We previously used 16S-based metagenomics to evaluate the microbiome from the vaginal introitus, midvagina, and posterior fornix of pregnant women at varying gestational ages. Notably, the vaginal microbiome differed based on proximity to the posterior fornix and by gestational age. (20) Moreover, there was an increase in *Lactobacillus* species in women who were pregnant compared with those who were not. Specifically, *Lactobacillus*

*jensenii* is known to anaerobically metabolize glycogen, which is at higher levels in pregnancy because of elevated estrogen levels. Thus, the increased expression of this bacteria and its associated metabolism of glycogen leads to a consistent acidic vaginal environment that likely prevents the development of dysbiosis such as bacterial vaginosis. (19) Notably, the prevention of dysbiosis can prevent infections that may be associated with preterm birth.

Interestingly, the vaginal microbiome becomes more similar to that of nonpregnant women during late gestation, which could be a signal to the body to initiate parturition. (20) Thus, the changes in the vaginal microbiome during pregnancy may help sustain the pregnancy, and dysbiosis of the “normal” vaginal microbiome may potentially lead to preterm labor and birth.

#### Development of the Neonatal Microbiome

It has traditionally been stated that the fetus resides in an in utero sterile environment. This theory postulates that as a neonate is born, it acquires bacteria via the maternal vaginal

tract and skin flora, which leads to the colonization of the neonate. In fact, previous consensus viewpoints held that microorganisms in fetal membranes were universally associated with infection and led to adverse pregnancy outcomes such as preterm birth, chorioamnionitis, and PPROM. While infection does arise from pathogenic bacteria, the identification of commensal microorganisms in these tissues by multiple investigative teams using sound methodology suggests that a microbe in the intrauterine environment does not cause inflammation or infection. Instead, contrary to the so-called “sterile womb” theory, numerous lines of evidence have converged to show that the first exposure to microorganisms may occur in utero and not at the time of birth per se. (14)(20)(21)(22)(23)(24)(25)

However, it remains unclear whether the fetus is truly colonized or is simply exposed to microorganisms and their products with this earliest in utero microbial exposure. We will now review the evidence supporting metagenomic detection of intrauterine microbes, and common associations with the development of the neonatal microbiome, such as the mode of delivery, the impact of maternal diet, the decision to formula or breastfeed, and the impact of the gestational age at the time of birth.

### The Low-Biomass, Low-Abundance Placental and Amniotic Microbiome

The vaginal microbiome is not the only microbiome that has been studied in the context of pregnancy. Our laboratory provided the initial characterization of the placental microbiome, which many others have replicated and expanded upon. (14)(26)(27) Key findings by multiple groups are that the placental microbiome is of low biomass and relative low abundance, that it bears greatest (but not absolute) similarity to the oral microbiome but is more distant from the stool and vaginal communities, and that it varies further by sublocalization in the placenta. (28) Further supporting this notion, bacteria present in amniotic fluid from pregnant women who deliver preterm are more likely to be from the oral cavity than the vagina. (29)(30) Other groups have shown that cultivation of both placental and amniotic fluid microbes is possible, (31)(32) though we and others have limited our interrogations to metagenomics. When one considers the ample evidence that the uterine decidua and other reproductive tissues manifest similar taxa in their low-biomass microbiomes, (33)(34) it is not surprising that the placental villi that implant in these same regions share these microbial taxa. (14)(24)(27)

Murine studies have demonstrated that consumption of food contaminated with *Campylobacter rectus* and/or *Porphyromonas gingivalis* during pregnancy results in decreased

fecundity and higher resorption rates. (35) These same mice had significant inflammation within the placenta along with increased expression of toll-like receptor 4, a part of the innate immune response that recognizes lipopolysaccharide, a component of the outer membrane of gram-negative bacteria. (35) Therefore, hematogenous spread of bacteria from the oral cavity to the placenta must logically have occurred during pregnancy because that was the only period of exposure (Fig 1). These findings alongside those in humans suggest that preterm delivery may not exclusively arise from ascending infections of the upper genital tract but may result from pathobionts spreading via hematogenous sources such as the oral cavity and urinary tract. Further supporting this notion are numerous studies linking periodontal disease with preterm labor. (36)(37)(38)(39)

While investigative teams delve further into the manifestations and variations of the human microbiome during pregnancy, there are several paramount questions whose answers currently are evasive. First, are there specific bacteria (pathobionts in particular) that are more likely to lead to preterm labor and/or PPROM? Are there specific bacteria that are protective against preterm deliveries and may mitigate pathobiont colonization? What human host factors and/or environmental interactions are important in establishing a “normal” microbiome during pregnancy and mitigating harm? These and other questions are key areas of study by researchers who are trying to determine likely microbial etiologies of preterm labor. By finding these answers, potential preventive and therapeutic interventions can be developed to target prevention of preterm birth throughout the world.

### Mode of Delivery

Cesarean deliveries were first performed as early as the 1500s. Cesarean deliveries are now the most common surgery performed, with nearly 1 million infants born in the United States each year via cesarean delivery. Some studies have associated children born via cesarean with higher rates of asthma, atopic allergies, obesity, and type 2 diabetes mellitus. Interestingly, several recent meta-analyses and other studies question the strength of these observations. (40)(41)

Initially, it was published that the mode of delivery led to long-term differences in the structure of the neonatal and infantile microbiome. (42)(43)(44) However, more recent studies have shown that the human microbiome effectively differentiates at each body site by 6 to 8 weeks of age, and the impact of mode of delivery on the microbiome is minimal after age 2 months. (45)(46) Furthermore, it is unclear if these alterations occur because of the indication



for a cesarean delivery, rather than the mode of delivery itself. Cesarean deliveries occur because of a medical indication, and it is unclear whether this indication has an impact on the structure, function, and development of the microbiome. (45)(47)(48) Chu and colleagues found that when controlling for the maternal indication for cesarean delivery and other clinical factors, formula feeding and maternal diet appeared to have a lasting impact on the infant microbiome at 6 weeks of age. (45) One study that investigated the microbiome in tracheal aspirates of preterm neonates provides further evidence supporting the lack of a role for the mode of delivery on the long-term effect on the neonatal microbiome. (49) Interestingly, there were no appreciable differences between the communities isolated from the tracheal aspirates of extremely low-birthweight neonates born via cesarean or vaginal delivery. (49)

Thus, the question of whether mode of delivery has a significant long-term impact on the infant microbiome and potential disease pathogenesis is far less evident than initially suggested. (50)(51) Regardless, the more robust metagenomics studies suggest that if the mode of delivery does affect the neonatal microbiome, it is most likely because of the maternal indication for the delivery and may be limited in scope, with no detectable differences by 6 to 12 weeks of age. (45)(52)(53)

#### Neonatal Feeding Practices: Benefits of Breast Milk

The American Academy of Pediatrics has made strong recommendations to support the use of breast milk and breastfeeding practices compared with formula feeding in the vast majority of circumstances. (54) Breast milk contains maternal antibodies to aid in host defense for the neonate and has been shown to reduce the risk of infectious disease and mortality in neonates. But, are there differences in the neonatal microbiome related to the type of feeding that the neonate receives?

Consumption of breast milk has been shown to modulate the infant gut microbiome. (55) Breast milk itself contains its own unique microbiome that can contribute to the bacterial communities present in the neonatal gut microbiome. Furthermore, breast milk contains fatty acids, vitamins, minerals, and other factors, such as IgA, that can aid in the neonatal gut microbiome colonization and development through processes of enchainment and tolerance. (56)(57) One such factor was previously known as the “bifidus factor.” First discovered in 1926 by Schonfeld, the bifidus factor was found to promote the growth of a protective commensal—*Bifidobacterium bifidus*. (58) What was previously known as the “bifidus factor” is now

more commonly known as human milk oligosaccharides (HMOs).

HMOs provide numerous health benefits to the neonate such as enhancing the growth of *Bifidobacterium longum* subspecies *infantis* (*B. infantis*), which serves as a commensal organism and prevents the growth of pathogenic bacteria in the neonatal intestine. (59) Furthermore, HMOs promote intestinal barrier function; prevent the adhesion of viral, bacterial, and protozoan pathogens within the intestine; and serve as decoy attachment receptors for pathogens, thereby preventing and reducing neonatal infections. (60)(61) The ability of HMOs to prevent the attachment and entry of pathogens is suggested to be one of the reasons why vertical transmission of HIV is inefficient and fewer than 10% of neonates acquire it through breastfeeding. (62)

Breast milk contains bacteria that would commonly be attributed to the skin and enteric systems: *Streptococcus*, *Staphylococcus*, *Escherichia*, *Enterococcus*, *Serratia*, and *Corynebacterium*, but notably, the microbiome of an individual's breast milk changes over time. (63)(64) Interestingly, colostrum has the greatest bacterial diversity that decreases as the milk matures, and the overall breast milk microbiome varies, based on maternal BMI. (63) Markedly, higher rates of *Staphylococcus* and lower rates of *Bifidobacterium* were present in obese mothers compared with women with normal BMIs at 6 months of lactation. (63)

Overall, breast milk microbiota improve neonatal immune function, improve intestinal barrier function, and enhance nutrient metabolism. However, the extent to which the breast milk microbiota is transferred to the neonate as well as the function of these bacteria is still unclear. By finding these answers, it may be possible to potentially manipulate the breast milk and/or neonatal microbiomes to target improvements in the health and outcomes of both mothers and their neonates.

#### The Impact of the Maternal Diet

The maternal diet affects not only the mother's own microbiome but also that of the offspring. (65) The maternal gut microbiome is significantly modified based on the maternal diet. Pregnant women with a high-fat diet have lower levels of commensal enteric bacteria such as *Bacteroides*. (65)(66) Animal models have shown that *Bacteroides* is vital for normal immune development within the intestines. (67) Therefore, lacking these commensals during pregnancy has been postulated to have lasting effects on the neonate such as predisposing them to atopic and autoimmune disorders later in life. (67)

Moreover, studies have elucidated that the breast milk microbiome varies simply based on the maternal BMI, with

obese mothers having higher quantities of *Staphylococcus* and *Lactobacillus* and lower counts of *Bifidobacterium* compared with mothers with normal BMIs. (63) However, maternal high-fat diet also increases milk fat concentration in breast milk compared with a diet high in carbohydrates. (68) With alterations of the breast milk microbiome as well as the macronutrient profile, it is likely that certain bacteria will have a predilection for this environment over others in the neonatal gut microbiome. The difference and potential increased expression of certain bacteria over others in the neonatal gut microbiome has not been extensively studied and is an open question in the field of metagenomics.

### Gestational Age at Birth

The effect of gestational age at birth and the impact on the neonatal microbiome cannot be underscored enough. Although prematurity in itself is associated with poorer short- and long-term outcomes for the neonate compared with term delivery, there are equally significant effects on the neonatal microbiome. (69)(70)(71)(72)

Premature neonates have higher levels of facultative anaerobic microorganisms and decreased levels of strict anaerobes such as *Bifidobacterium* and *Bacteroides*. (73) *Bifidobacterium* is considered a “healthy” commensal organism that helps prevent the residence of pathogenic bacteria. Therefore, premature neonates have delayed colonization with these healthy commensals and a propensity for colonization with pathogenic bacteria. As such, *Klebsiella*, *Enterobacteriaceae*, *Staphylococcus*, *Streptococcus*, and other virulent bacteria have been found more commonly in the microbiomes of premature neonates than in term neonates. (74) Notably, the predilection for the premature neonatal gut microbiome to harbor these pathogenic bacteria is highest for very early preterm infants (23–30 weeks), and the presence of *Bifidobacterium* is associated with increased gestational and postnatal age. (75)(76) Furthermore, the presence of *Bifidobacterium* has been considered protective against the development of NEC, but this is currently controversial because its presence may be simply a marker of intestinal maturity rather than a protective mechanism. (77)

### Summary

Although influenced by these aforementioned exposures as well as others such as antibiotic and environmental exposures (Fig 2), the neonatal microbiome develops and expands exponentially after birth. Although it is unclear whether the in utero exposure to microorganisms leads to colonization versus simple exposure, neonates are born with detectable microorganisms. The initial bacterial species within the neonatal intestinal microbiome are mainly

composed of *Streptococci*, *Lactobacilli*, and *Enterobacteriaceae*. (78) Although there are some potential differences within the neonatal microbiome initially based on mode of delivery, these effects are no longer appreciable by 6 weeks of age. (45) Instead, the microbiome develops “niche specificity” based on specific parts of the body and continues to diversify and expand to become more adultlike over the course of the first year.

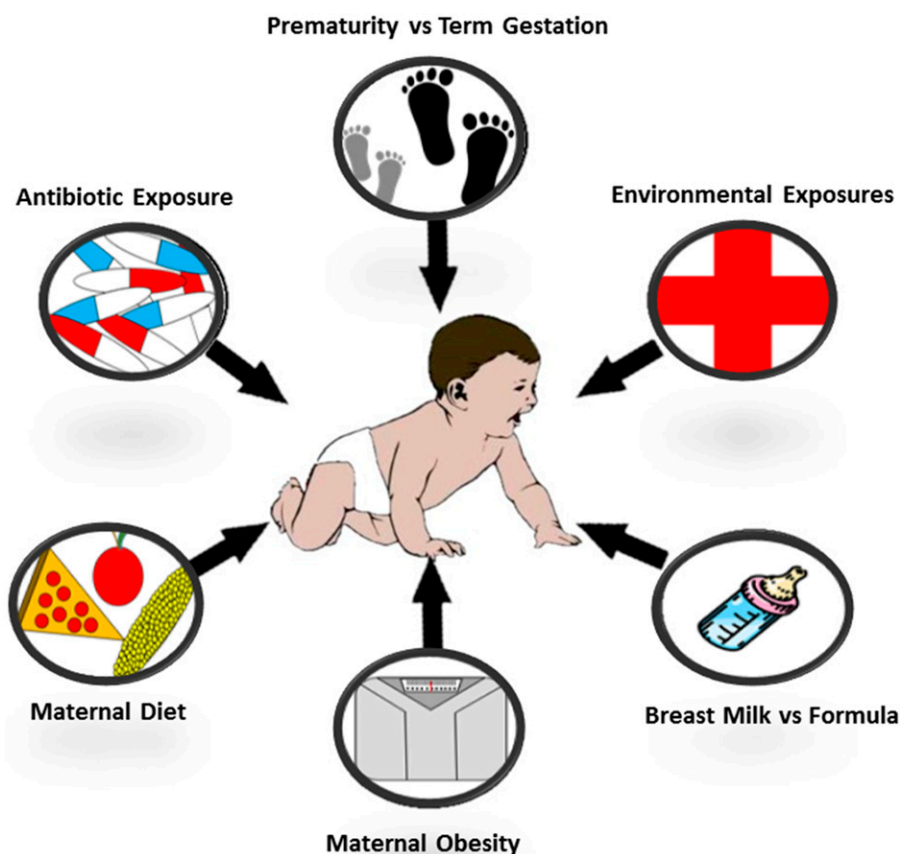
## FRIEND OR FOE: WHAT HAPPENS WHEN DYSBIOSIS OCCURS?

What happens when the “normal” colonization and formation of the human microbiome goes awry? Dysbiosis of the human microbiome has been associated with numerous disease states such as inflammatory bowel disease, obesity, irritable bowel syndrome, type 2 diabetes, and colorectal cancer. (79)(80)(81) The DOHaD hypothesis suggests that microbial perturbations early in life can lead to chronic medical conditions later. Thus, the development of the microbiome in the neonate is a keen area of interest among researchers because of this critical transition period from a low-biomass “womb” to encountering the trillions of bacteria present in the everyday world. We now review group B *Streptococcus* carriage in the pregnant woman and the effect on the neonate; then we conclude with a discussion on dysbiosis and its relationship to the development of NEC.

### Group B *Streptococcus* Infection

*Streptococcus agalactiae*, commonly known as group B *Streptococcus* (GBS), is one of the most common causes of neonatal sepsis, pneumonia, and meningitis. When deciding if a bacterium is a “friend” or a “foe,” GBS, a gram-positive  $\alpha$ -hemolytic bacterium, is commonly grouped in the “foe” category because of the life-threatening disease it can cause in neonates. However, in pregnant women, it rarely causes disease and serves more as a commensal organism, though potential links to preterm birth have been found (Fig 1). (26) Because 10% to 30% of pregnant women are known to be colonized with GBS, the current recommendations by the American College of Obstetricians and Gynecologists are to universally screen pregnant women at 35 to 37 weeks’ gestation or those with preterm labor or PPRM in efforts to determine which women should receive antibiotic treatment to prevent the vertical transmission of GBS to the neonate. (82)

With the advent of this universal screening approach and the treatment with antibiotics for women who test positive for GBS carriage, neonatal infection and death by GBS have been dramatically reduced for early-onset disease.



**Figure 2.** The impact of maternal and environmental factors on the development of the neonatal microbiome. The neonatal microbiome is influenced by numerous factors such as maternal and postnatal antibiotics, maternal diet, maternal obesity, breast milk and/or formula feeding, environmental exposures such as those within the NICU, and gestational age. Of note, the microbiome varies considerably with pathogenic microbes favoring the premature gut microbiome and healthy commensals such as *Bifidobacterium* favoring the term neonatal gut microbiome. Many factors are not independent and interact with each other. For instance, maternal diet can contribute to maternal obesity, which has effects on the maternal and breast milk microbiome, all of which directly affect the development of the neonatal microbiome.

Interestingly, there has also been a proportionate increase in the number of neonatal deaths attributable to  $\beta$ -lactam-resistant *Escherichia coli* in very-low-birthweight (VLBW) and premature neonates. (83) Thus, the overall rate of early-onset sepsis has not significantly decreased since the advent of the universal screening and treatment recommendations for GBS, but the etiology of the pathogens causing early-onset sepsis has changed along with an increased resistance pattern among these organisms. (84) Furthermore, the incidence of late-onset GBS disease in neonates has not changed with the advent of intrapartum prophylaxis for GBS in pregnant women. Thus, while GBS serves as a likely commensal in adult women, it can serve as a potential pathogen in the neonate—a key reminder that while bacteria may serve as “foes” in certain situations, this is not always true in every situation.

### Necrotizing Enterocolitis

NEC affects approximately 7% of VLBW neonates and has an associated mortality rate of 20% to 30%. As such, NEC is a

leading cause of morbidity and mortality among premature neonates. However, recent evidence has supported the use of exclusive human milk diets and donor human milk to decrease the rates of NEC significantly among the premature neonatal population. (85)(86)(87) Regardless, dysbiosis of the intestinal microbiome has been shown to be associated with NEC in preterm infants and in animal models. (88)

Stewart and colleagues discovered that intestinal bacterial communities in infants with NEC and late-onset sepsis were different from those seen in healthy preterm infants. The presence of *Enterobacteria* was associated with the development of NEC whereas the presence of *Staphylococcus* was associated with late-onset sepsis. (88) In contrast, Normann and colleagues evaluated the microbiome in fecal samples of 20 preterm neonates, 10 with NEC and 10 healthy controls. Interestingly, no significant differences were found in the fecal microbiomes of the 2 groups. (89) Thus, the evidence supporting a single causative bacterial pathogen as responsible for NEC is lacking. Rather, NEC may develop as a result of dysbiosis or generalized

disturbance in the normal development of the gut microbiome. (86)

Further supporting dysbiosis relating to NEC, prospective studies have found discernible changes in the microbiome of infants before the development of NEC. (90) Phyla-level shifts in the microbiome occur between 3 and 7 days before the diagnosis of NEC. (90) Moreover, using principal coordination analysis, Stewart and colleagues discovered that fecal samples obtained before the diagnosis of NEC showed a distinct clustering of the microbiome compared with healthy controls. (88) Thus, while a single bacterium does not appear to be the causative agent for the development of NEC, an alteration of the normal development of the premature neonatal intestinal microbiome may elicit alterations in the host immunity and/or intestinal barrier function, ultimately leading to the development of NEC. Further studies are necessary to investigate and determine this potential role of dysbiosis in triggering changes in intestinal barrier function and the development of NEC.

## FUTURE DIRECTIONS AND UNANSWERED QUESTIONS

Although numerous advances have been made in the field of metagenomics, many questions remain. Inevitably, as researchers seek and find answers to these questions, new questions arise.

### Fetal Colonization or Microbial Exposure?

One paramount question whose answer remains elusive is whether the fetus is merely exposed to microorganisms (as detected metagenomically) or is truly colonized in utero. Exposure to microorganisms has been shown to lead to immune priming of the gut. It is possible that the organisms discovered by metagenomic methodology are simply pieces of dead bacteria that serve to prime the fetal immune system. Another possibility is that these genetic bacterial signatures found in the amniotic fluid are actual live bacteria that may serve as the initial colonization of the future neonatal microbiome. To date, our evidence supports the former but neither supports nor refutes the latter.

### Dysbiosis and the Development of Disease

Although dysbiosis has been linked to several key diseases such as inflammatory bowel disease, irritable bowel syndrome, atopic conditions, and NEC, what about other diseases? Disruptions in the microbiome have been associated with these diseases, but causal relationships have yet to be firmly established in most cases. Both environmental and host modifiers must be better defined to evaluate these associations.

Furthermore, in cases in which disease states have been associated with perturbations of the microbiome, is there a critical period of microbiome development that, if disrupted, leads to the disease state? Are there potential bacteria that may be protective against the development of that disease state? Also, are there ways to revert the disease state back to a healthy state with fecal transplantation or probiotics? By seeking the elusive answers to these key questions, targeted investigational and therapeutic approaches can be developed to potentially prevent and/or treat diseases related to the dysbiosis of the human microbiome.

## CONCLUSION

With the advent of metagenomics, we can characterize the developing microbiome community structure and function. Although cultivation-based methods were previously the golden standard to evaluate the microbiota, there are significant limitations with the lack of ability to detect fastidious and low-abundant organisms. The field of metagenomics can detect organisms not grown by culture-based means and also properly evaluate and determine levels of these previously underevaluated organisms. Because of metagenomics, dogmas such as the “sterile womb” theory are challenged due to the discovery of microorganisms in these tissues previously considered sterile. However, it is unclear if these bacteria truly colonize the fetus or are transiently present for priming of the fetal immune system.

The neonatal microbiome develops over the course of the first few years of age, with an expanding diversity of bacterial flora that develop into specific body niches. Interestingly, while the mode of delivery was previously considered a significant factor in altering the development of the neonatal microbiome, further studies have shown that this may not be the predominant factor influencing the establishment and development of the offspring microbiome. Instead, the neonatal microbiome is predominantly influenced by maternal diet, breastfeeding versus formula feeding, and gestational age.

Perturbations in the neonatal microbiome can lead to potential significant health consequences and disease states. In the pregnant woman, the presence of GBS can lead to sepsis and potential mortality in the neonate. In the neonate, dysbiosis of the intestine can lead to NEC. However, although the advent of metagenomics has led to characterization of the healthy and dysbiotic microbiomes, many questions remain. Through the discoveries of metagenomics, hypothesis-driven research is important to further interrogate disease pathogenesis; this will have a significant

impact on the prevention and treatment of disease through manipulation of the human microbiome.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Identify the risk factors, including the effects of choriodecidual pathogens and resulting inflammation, as contributing factors for preterm birth.
- Know the causes, complications, and management of preterm premature rupture of membranes.
- Know how body composition changes during postnatal growth and development and understand the effect of prematurity.
- Know the pathophysiology of necrotizing enterocolitis.

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1. The microbiome and its dysbiosis are emerging as important mitigators of long-term health in humans. Which of the following disorders has NOT been linked to dysgenesis of the microbiome?
  - A. Inflammatory bowel disease.
  - B. Obesity.
  - C. Colorectal cancer.
  - D. Type 1 diabetes.
  - E. Eczema.
2. During pregnancy, the fetus is exposed to the microorganisms of the placenta, amniotic fluid, and vaginal microbiome. Which of the following statements regarding these prenatal exposures is CORRECT?
  - A. *Lactobacillus* species increase in the vaginal microbiome of pregnant women because of elevated progesterone levels.
  - B. The placental microbiome is characterized by low-biomass, high-abundance bacterial communities.
  - C. The placental microbiome is more similar to the oral microbiome than it is to the vaginal or gut microbiomes.
  - D. The ability of *Lactobacillus jensenii* to anaerobically metabolize glycogen and acidify the vaginal environment is thought to be an important factor in the prevention of vaginal dysbiosis.
  - E. The vaginal microbiome becomes more similar to that of nonpregnant women during late gestation.
3. Our understanding of the development of the microbiome in the neonatal period has increased rapidly in recent years because of several technological advances. Which of the following statements regarding the techniques currently available to study the human microbiome is CORRECT?
  - A. Culture-based methodologies have limited usefulness because as much as 50% of bacteria will not grow in standard bacterial media.
  - B. 16S ribosomal RNA (16S rRNA)-based techniques classify the phylogeny and taxonomy of bacteria based on 6 hypervariable regions (V1-V6).
  - C. The 16S rRNA technique has been shown to overestimate *Bacteroides*.
  - D. Whole genome shotgun (WGS) techniques allow for the detailed taxonomic classification of bacterial species but cannot be used to assess the metabolic capacity of bacterial species.
  - E. Because not all organisms have reference genomes, de novo assembly of the microbial genomes occurs commonly and is a limitation of WGS techniques.
4. The neonatal microbiome is influenced by multiple perinatal factors, including mode of delivery, maternal diet, formula or breastmilk feeding decisions, and gestational age at birth. Which of the following statements regarding the development of the neonatal microbiome is CORRECT?
  - A. The presence of *Bifidobacterium* in the neonatal gut microbiome is associated with increased gestational age at birth but not postnatal age.
  - B. The breast milk microbiome of obese mothers is characterized by lower quantities of *Lactobacillus* and higher counts of *Bifidobacterium* compared with that of mothers with a normal body mass index.
  - C. The bacterial diversity in breast milk is highest in colostrum compared with mature milk.
  - D. The gut microbiome of pregnant women with a low-fat diet is characterized by lower levels of commensal enteric bacteria, such as *Bacteroides*.
  - E. Cesarean deliveries affect the structure of the microbiome well into early childhood.

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5. Dysbiosis of the human microbiome has been associated with multiple disorders such as inflammatory bowel disease and obesity, as well as metabolic and atopic disorders. In the neonate, dysbiosis has been linked to the development of necrotizing enterocolitis (NEC). Which of the following statements regarding the pathophysiology of NEC is INCORRECT?
- A. The use of exclusive human milk diets has significantly decreased the rates of NEC among preterm neonates.
  - B. The presence of *Enterobacteria* has been associated with the development of NEC in multiple large cohort studies.
  - C. Phyla-level shifts in the microbiome occur between 3 and 7 days before the diagnosis of NEC.
  - D. The presence of *Staphylococcus* in the intestinal microbiome is associated with late-onset sepsis but not NEC.
  - E. A causal relationship has yet to be firmly established between dysbiosis and NEC.

# The Neonatal Microbiome and Metagenomics: What Do We Know and What Is the Future?

Gregory Valentine, Amanda Prince and Kjersti M. Aagaard

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# Genetic Approaches to Bronchopulmonary Dysplasia

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## Education Gap

Bronchopulmonary dysplasia (BPD) remains a challenging complication of prematurity for neonatologists. Although our understanding of this disease process has increased over time, significant attention has been paid to modifiable factors such as antenatal steroids, as well as postnatal ventilation and nutritional strategies. Still underappreciated, however, is the genetic predisposition to the development of BPD. This article summarizes various studies that have attempted to investigate gene-environment interactions related to BPD.

## Abstract

Bronchopulmonary dysplasia (BPD) remains a common and challenging complication of prematurity, with limited effective strategies at the neonatologist's disposal. Throughout the years, our understanding of this complex syndrome has broadened. Instead of solely attributing this disease to the effects of prematurity and injuries to the lung from mechanical ventilation, it is now accepted to be a multifactorial disease. Recent research efforts have focused on investigating the gene-environment interactions that may influence an infant's susceptibility toward the development of BPD. So far, success has been limited but promising, offering hope that in the future, novel therapies will be available to ameliorate the risk for BPD.

## Objectives After completing this article, readers should be able to:

1. Explain the difference between "old" and "new" BPD.
2. Describe the contribution of genetics to the development of BPD.
3. Explain the proposed role of microRNA in the development of BPD.

## INTRODUCTION

Bronchopulmonary dysplasia (BPD) is an extremely common chronic lung disease during infancy, and the incidence has continued to rise with the increasing

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### ABBREVIATIONS

BPD	bronchopulmonary dysplasia
GWA	genome-wide association
miRNA	microRNA
NICHD	National Institute of Child Health and Human Development
RISC	RNA-induced silencing complex
SNP	single nucleotide polymorphism
VLBW	very-low-birthweight



survival of extremely premature neonates. (1) With limited options for effective and sustained postnatal therapeutic interventions, it continues to be a frustrating clinical syndrome for neonatologists. Initially described by Northway et al in 1967, the advent of mechanical ventilation in preterm neonates has led to an evolution of the definition and characteristics of BPD over the past 50 years. (2) Once thought to predominantly stem from insults to the lung, BPD is now believed to result from an impairment in lung development. The “classic” form of BPD, characterized by airway injury, pulmonary edema, inflammation, fibrosis, and smooth muscle hypertrophy, was largely attributed to prolonged mechanical ventilation and oxygen exposure in the preterm infant. (3) Over time, this has transitioned into the concept of “new” BPD, characterized by a progressive deterioration in pulmonary function, a significant decrease in alveolarization and vasculogenesis, and heterogeneous, coarse densities in the lungs. (1)(4)(5) Since June 2000, the diagnosis of BPD has changed from an assessment of an oxygen requirement at 28 days of age, to the current severity-based stratification occurring at 36 weeks’ postmenstrual age, which defines BPD based on the infant’s ongoing need for respiratory support. (6) (7) However, despite this more nuanced definition, it has become apparent that BPD is a diverse and variable disease, not only between infants, but even within the same infant throughout his or her clinical course.

The morbidity and mortality associated with BPD is significant, with affected infants showing persistent pulmonary impairment even as children and adults. Infants with BPD have a higher risk of developing asthma and of requiring hospitalization for pulmonary exacerbations, as well as developmental disorders, all leading to higher health-care costs. (1) Consequently, many studies have focused on addressing the pathophysiology of BPD and its possible management. Despite advances in neonatal-perinatal medicine, including antenatal steroid use, postnatal surfactant therapy, and various ventilation strategies, BPD remains a serious and persistent clinical problem. (8) As with other common complications of prematurity, the development of BPD is multifactorial, with an infant’s predisposition, outcome severity, and treatment response widely believed to be affected by complex gene-environment interactions. As such, various approaches have aimed at identifying specific genes or pathways that could be implicated in the development of BPD.

## TWIN STUDIES AND BPD

Multiple studies have used twin cohorts to address genetic and environmental influences on preterm birth outcomes,

including BPD. Although some researchers have looked at the effects of birth order, gender, and intrauterine growth restriction on mortality and morbidity rates of very-low-birthweight (VLBW) twins, in 1996, Parker et al was one of the first groups to retrospectively examine the occurrence of BPD among twins. (9) Even after adjusting for birthweight, gestational age, gender, severity of respiratory distress syndrome, patent ductus arteriosus, pneumothorax, infection, and antenatal steroids using multiple logistic regression modeling in 108 VLBW twin pairs, the authors showed that there was significant concordance of BPD status between twins. (9) When BPD was diagnosed in the first-born twin, it also occurred in 65% of the second-born twins. In contrast, when BPD was not diagnosed in the first-born twin, only 8% of the second-born twins were diagnosed with BPD. (9) Although zygosity could not be established to delineate the effects of genetics from shared environmental factors, this novel study strongly suggested that BPD has a genetic component.

In 2006, Bhandari et al expanded this hypothesis by investigating 252 preterm twin pairs across 4 institutions. (10) Not only was the concordant development of BPD between twins supported, but the authors also analyzed a subgroup for which zygosity was available. Although twins typically share the same in utero environment and often similar postnatal treatments, monozygotic twins are unique in having a higher number of shared genes compared with dizygotic twins. Therefore, a higher incidence of similarities between monozygotic twins implies the presence of a genetic component. After adjusting for multiple demographic factors, Bhandari et al demonstrated that monozygotic twins were more likely than dizygotic twins to develop BPD and require a longer stay in the NICU. (10) They showed that genetic factors are a significant contributor to BPD, proposing that these factors account for 53% of the observed variance. (10)

A new definition of BPD was proposed in 2000 by the National Institute of Child Health and Human Development (NICHD)/National Heart, Lung, and Blood Institute Workshop based on gestational age and severity (which was clinically validated by Ehrenkranz et al in 2005). (6)(7) Lavoie et al estimated heritability in 159 preterm twin pairs by calculating the contributions of genetic, shared environmental, and nonshared environmental factors. Using model-fitting analyses, the authors found an even stronger genetic component for 36-week oxygen need-based BPD and NICHD-defined BPD compared with previous studies. (11) However, a 2018 study by Parad et al using chorionicity as an indicator of zygosity showed no significant heritability pattern in 183 preterm twin pairs. (12) The infants included

in this study were born at lower gestational ages and birth-weights compared with infants in previous studies. The role of genetics in the development of BPD continues to be an ongoing topic of research. A response letter by Bhandari et al has been accepted for publication by the *Journal of Pediatrics* (direct communication, January 2019). Overall, the heritability component from most of these twin studies is estimated to be between 50% and 80%, strongly suggesting that genetic influences play a role in the development of BPD. Despite this, no specific genes or heritable factors have been successfully identified.

## GENETIC STUDIES AND BPD

The human genome is a complex organization of approximately 20,000 genes that encode proteins, as well as a variety of noncoding regulatory components. Only about 0.1% of the genome differs between individuals, contributing to variability. This manifests phenotypically with variations in characteristics such as height or eye color but is also thought to contribute to differences in disease susceptibility. Although some disease-causing mutations are severe, these typically occur in specific genes and are overall rare. Much more prevalent, but less understood, are minor sequence variations that may have subtle influences on the predisposition to disease development. The most common of these are single nucleotide polymorphisms (SNPs), which are individual base-pair substitutions that occur in approximately 1 in 1,000 base pairs. Starting in 2002, international researchers collaborated to create a haplotype map, known as the International HapMap Project (<https://www.genome.gov/10001688/international-hapmap-project>), which was aimed at cataloging common SNP variations in the human genome.

Genome-wide association (GWA) studies are used to widely examine millions of SNPs between a “diseased” population and a “control” population, and have been successfully used in diseases such as diabetes, Crohn disease, and coronary artery disease. (13) This is inherently more difficult in the analysis of BPD because GWA studies are dependent on a large sample size and the presumption that the at-risk, or diseased, alleles, will be passed on to the patients’ offspring often enough to affect the frequency. However, BPD is a major cause of neonatal mortality, limiting the inheritability rate of the at-risk alleles.

To date, 3 GWA studies on BPD have been published. In 2011, Hadchouel et al analyzed 418 extremely premature infants of Caucasian-French or African-French descent, and found that allele C of the rs1245560 SNP of the *SPOCK2* (SPARC/osteonectin, CWCV, and Kazal-like domains

proteoglycan 2) gene was significantly associated with moderate-severe BPD even after adjustment for perinatal factors. (14) These findings were replicated in a Finnish cohort by the same authors, who also showed that *SPOCK2* mRNA was significantly increased during the alveolar stage of development in rat pups, particularly when they were exposed to hyperoxia. (14) Wang et al performed a GWA study on 1,726 VLBW extremely premature infants, predominantly of Mexican-Hispanic origin. Their data did not show any SNP to have a statistically significant association with BPD, including those from prior studies. (15) The most recent study, by Ambalavanan et al, used 834 infants to combine their GWA with pathway-based approaches, including early death as a competing outcome for BPD. No SNP was found to be significant in any of their comparisons, but a few were close to statistical significance, including adenosine deaminase (ADARB2) and CD44. However, their data were notable for the implication that the pathways associated with severe BPD or overall death are different from those for mild or moderate BPD. (16)

In contrast to GWA research, candidate gene studies focus on polymorphisms for specific genes that are hypothesized to be involved in the development of particular diseases. In the case of BPD, success has been limited, partly because of small sample sizes but also the prevailing idea that BPD is likely to be polygenic. There are published results for genes encoding for surfactant proteins, mannose-binding lectin, tumor necrosis factor, interferon  $\gamma$ , angiotensin-converting enzyme, interleukins, growth factors, superoxide dismutases, toll-like receptors, macrophage migration inhibitory factor, human leukocyte antigens, and vascular endothelial growth factor, among others. Overall, these have had inconsistent results. Although some studies may express significant results for a particular gene, the results have generally not been reproducible, with statistical significance eliminated when using larger sample sizes in follow-up studies. (17)

## MICRORNAs AND BPD

A more recent genetic approach has focused on small genomic components known as microRNAs (miRNAs), which are a relatively new family. First discovered in the 1990s in *Caenorhabditis elegans*, miRNAs are endogenous, single-stranded, noncoding RNAs that are only about 20 nucleotides in length. It was initially believed that there were approximately 200 to 1,000 miRNA genes in the mammalian genome, contributing to 1% to 3% of known genes, but as of 2018, there are more than 2,000 just in the human genome. (18) Recent discoveries have shown that

after transcription and processing in the nucleus, and subsequent exportation to the cytosol, mature miRNA is incorporated into the RNA-induced silencing complex (RISC). The RISC post-transcriptionally regulates gene expression via partial or complete complementarity to the 3' untranslated region of target mRNA molecules. Depending on the level of complementarity, this process results in an inhibition of the initiation of translation, an inhibition of peptide elongation, or an induction of mRNA degradation (Fig). (19)(20) In the past 2 decades, miRNAs have been found to play important roles in various biological processes such as developmental timing, proliferation, differentiation, signaling, inflammation, tissue morphogenesis, and cell death. In addition, they have been implicated in a wide variety of diseases, such as cancer, cardiovascular diseases, and a number of childhood diseases, including pediatric respiratory diseases. Early studies have shown a change in expression of a few miRNAs during lung development. (21)

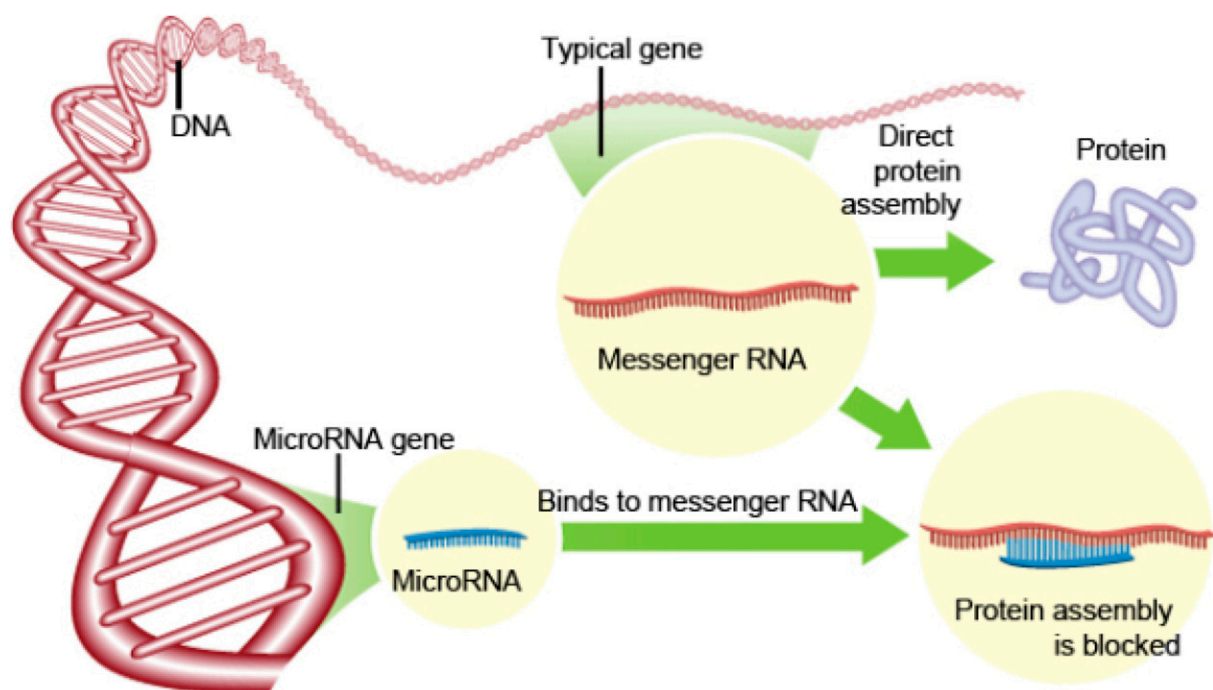
A meta-analysis of 3 independent studies found that a number of miRNAs showed changes in expression when BPD lung tissues were compared with control groups. (22) Dravet-Gounot et al identified 13 miRNAs with differential expression between the lungs of rat pups with intrauterine growth restriction and control rat pups, with their data suggesting that the changes in lung miRNA would impair

alveolarization. (23) Subsequent studies in mice identified miRNA-489 as a possible inhibitor of alveolar septation, (24) while miRNA-29b supplementation improved alveolarization. (25)

In 2015, Rogers et al showed that expression of the *miRNA-17~92* cluster, which contains 6 individual miRNAs, is significantly decreased in autopsy lung tissues of infants who died with BPD, and in the plasma of infants subsequently diagnosed with BPD, compared with control infants. (26) It has previously been shown that the *miRNA-17~92* cluster is essential to normal lung growth and development, and that whole-genome *miRNA-17~92* cluster deletion is lethal because of an inability to develop lung epithelial cells. (26) A subsequent study correlated the severity of BPD to the level of decrease in the expression of the *miRNA-17~92* cluster, with the most significant decreases seen in infants diagnosed with severe BPD. (27)

Syed et al demonstrated that miR-34a levels are significantly increased both in the lungs of neonatal mice and in type 2 alveolar epithelial cells of infants exposed to hyperoxia. (28) In addition, miR-34a overexpression worsens the pulmonary phenotype and BPD-associated pulmonary arterial hypertension in BPD mouse models. (28)

Most recently, a number of miRNAs have been implicated in the regulation of a process known as macroautophagy (hereafter referred to as autophagy) and these



**Figure.** MicroRNA schematic. MicroRNAs are small, endogenous, noncoding RNAs that post-transcriptionally regulate gene expression via partial or complete complementarity to the 3' untranslated region of target mRNA molecules. This process results in an inhibition of the initiation of translation, an inhibition of peptide elongation, or an induction of mRNA degradation.

miRNAs are beginning to be considered as novel therapeutic targets for lung diseases. (29) It has been previously shown that autophagy is induced by hyperoxia in lung epithelial cells and neonatal mouse lungs, and thus, appears to play an important, protective, antiapoptotic role in the development of BPD. (30) It has been reported that autophagy can inhibit or promote cell death in both developmental and diseased conditions, including cancer, neurodegenerative disorders, and metabolic and infectious diseases. (31) The deletion of essential autophagy genes (beclin [*BECN*] 1, and autophagy-related [*ATG*] 5) in mice causes early embryonic or neonatal lethality, underscoring the importance of autophagy to the developmental process. Researchers also believe that autophagy is involved in the pathogenesis of various preclinical models of pulmonary diseases, in cell lines and the murine model, as well as in humans. (30)

The complex process of autophagy is regulated by a diverse network that consists of different signaling pathways and autophagy-related genes, which were first discovered in the 1990s in yeast. Much of the known regulation occurs at the post-translational level, predominantly via phosphorylation or acetylation, but transcriptional control of autophagy genes is an area of more recent research. Recent literature has focused on the regulation of autophagy via miRNAs. (29) Preliminary data presented at American Thoracic Society in 2018 proposed that miRNA-99 modulates autophagy by specifically targeting the protein kinase B/mechanistic target of rapamycin signaling pathway, which is known to be a negative regulator in the initiation of the autophagy pathway. (32)

## CONCLUSION

There have been many advances in neonatal-perinatal medicine over the past 40 years that have significantly improved the survival of extremely premature neonates. Yet unfortunately, complications of prematurity persist, with limited successful interventions in some conditions such as BPD. It is well understood that lung development is a complex process that is dependent on various genes, but our comprehension of how genes affect BPD is still in its infancy. Multiple studies using various approaches have strongly supported the idea of a genetic basis for the development and severity of BPD; however, further research is needed to identify specific genes in the BPD pathway that can be targets for therapeutic intervention. The hope is that with a greater understanding of the gene-environment interaction, therapies can be individually tailored to infants.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathogenesis, pathophysiology, and pathologic features of bronchopulmonary dysplasia/chronic lung disease.
- Know the prenatal and postnatal risk factors for bronchopulmonary dysplasia/chronic lung disease and be aware of various preventive strategies.
- Know the management of bronchopulmonary dysplasia/chronic lung disease.

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1. In investigations to assess the potential contribution of genetic factors that may play a role in the development of conditions such as bronchopulmonary dysplasia, the concordance of twin pairs in having the condition can give an indication of genetic risk. Which of the following principles is most relevant and applicable when evaluating such studies?
  - A. While it is an interesting hypothesis, there have been no studies that have demonstrated twin concordance in the development of bronchopulmonary dysplasia.
  - B. Twin studies cannot inform the question on genetic risk for bronchopulmonary dysplasia, because it is not possible to distinguish whether genetic factors or inflammatory factors contribute to disease concordance.
  - C. Monozygotic twins are unique in having a higher number of shared genes compared with dizygotic twins, and therefore, a higher incidence of similarities between monozygotic twins implies that a genetic component is present when there is higher disease concordance.
  - D. Although twin studies for bronchopulmonary dysplasia vary in the incidence of outcomes, heritability patterns appear to be strongest in the lowest birthweight and earliest gestational age categories.
  - E. Although epidemiologic twin studies have been inconclusive with regard to heritability patterns for bronchopulmonary dysplasia, several genes have been found that appear to have a predisposition for both twinning and bronchopulmonary dysplasia.
2. Genome-wide association studies to investigate bronchopulmonary dysplasia have examined millions of single nucleotide polymorphisms (SNPs) between those who have disease and those who do not. Which of the following statements concerning these studies is correct?
  - A. SNPs are base-pair substitutions that occur in approximately 1 in 1,000 base pairs.
  - B. SNPs represent major mutations that tend to have multiple downstream effects in several organ systems.
  - C. Several genome-wide association studies have consistently shown that an SNP now labeled as the *BPD1000* gene is a strong risk factor for the development of bronchopulmonary dysplasia.
  - D. An underlying principle of studies investigating SNP variation is that 99% of the genome differs among individuals.
  - E. A challenge in these studies is that there has been no uniform effort to catalog common SNP variations in the human genome.
3. In an effort to elucidate mechanisms of disease progression of bronchopulmonary dysplasia, candidate gene studies have been performed. Which of the following statements concerning these studies is correct?
  - A. Candidate gene studies use the variation in SNPs among individuals to identify the genetic link to disease.
  - B. Success of these studies has been limited partly because of small sample sizes and also the likelihood that bronchopulmonary dysplasia is likely to be polygenic.
  - C. The strongest link to bronchopulmonary dysplasia has been to genes encoding for atrial natriuretic factor.
  - D. Mutations in the *PE-BPD1* gene have been associated with both preeclampsia in the mother and bronchopulmonary dysplasia in the infant.
  - E. Candidate gene studies can be easier to perform than other genetic studies in that a specific candidate does not need to be identified before performing testing.

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4. A method of studying genetic contributions to bronchopulmonary dysplasia is using microRNAs. Which of the following statements describes this method correctly?
- A. microRNAs are derived from commensal bacteria.
  - B. microRNAs are coding segments that specifically relate only to cell nucleus function and structure.
  - C. microRNAs are typically 100 to 200 nucleotides in length.
  - D. There are more than 2,000 microRNAs in the human genome.
  - E. After transcription and processing in the nucleus, mature microRNAs remain solely in the nucleus, where they bind to other DNA and RNA segments.
5. In relation to genetic studies on bronchopulmonary dysplasia, the process of autophagy has been implicated in pulmonary disease. Which statement correctly describes the process of autophagy?
- A. Autophagy appears to be induced by hyperoxia in lung epithelial cells and neonatal mouse lungs, and may play an important, protective, antiapoptotic role in the development of bronchopulmonary dysplasia.
  - B. Autophagy is always a promoter of cell death and only functions in diseased conditions.
  - C. The regulation of autophagy occurs exclusively at the pretranslational level.
  - D. Autophagy appears to function independently from microRNAs.
  - E. Autophagy has replaced the term "apoptosis" to signify programmed cell death.

## Genetic Approaches to Bronchopulmonary Dysplasia

Melanie Leong

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# Navigating Newborn Screening in the NICU: A User's Guide

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## Education Gaps

1. Newborn screening consists of testing that is more extensive than just for phenylketonuria; current screening includes an increasing number of diverse disorders in which early intervention can lead to improved patient outcomes.
2. The timeliness of newborn screening is critical and a delay can lead to a late diagnosis, which can have serious health consequences.
3. Newborn screening involves screening for critical cyanotic congenital heart disease and hearing loss in addition to the heel test.

## Abstract

Newborn screening (NBS) is the largest public health program in the United States, affecting every newborn. The purpose of newborn screening is to identify newborns at risk for selected disorders during the presymptomatic phase, with the hope that early intervention can prevent disease progression. NBS began in the early 1960s following the pioneering work of Robert Guthrie with phenylketonuria. Since then, NBS has expanded, with testing available for more than 50 disorders in most states. Screening tests need to be highly automated, with high sensitivity and specificity to avoid missing patients with disease, and ensuring manageable false-positive rates. Current initiatives in NBS include timeliness to ensure that results of the screen are available by 5 days after birth for a core set of critical conditions. This has resulted in the current recommendation for *NBS specimens to be collected at 24 to 48 hours after birth*. False-positive rates are higher in the NICU, because of the metabolic instability of sick neonates and the immaturity of premature enzyme systems. The recommended uniform screen panel (RUSP) contains the current list of disorders screened for by most states. Additional disorders continue to be added to the RUSP as medical progress allows previously untreatable disorders to be managed successfully, and thus the need to screen emerges. The costs associated with NBS continue to climb, because despite state-mandated screening, the diagnostic evaluation and treatment

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### ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
BIA	bacterial inhibition assay
GAMT	guanidinoacetate methyltransferase
MCAD	medium chain acyl-CoA dehydrogenase
MS/MS	tandem mass spectroscopy
MSUD	maple syrup urine disease
NBS	newborn screening
PKU	phenylketonuria
RUSP	recommended uniform screen panel
SCAD	short-chain acyl-CoA dehydrogenase
SMA	spinal muscular atrophy

of these conditions has no such mandate. This is a particular concern for disorders with annual treatment costs of several hundred thousand dollars.

## Objectives After completing this article, readers should be able to:

1. Recognize the importance of timeliness in newborn screening.
2. List the reasons for false-positive newborn screening results in the NICU setting.
3. Recognize that the number of disorders on the newborn screening panel continues to grow.
4. Describe the newborn screening process that includes recommendations for additional testing occurring at the federal level with implementation at the state level.

## INTRODUCTION

Newborn screening (NBS) is the one of the largest public health initiatives in the United States, with more than 4 million infants being screened for over 50 disorders in the first few days after birth (Fig 1). The purpose of NBS remains the same since its initiation in the 1960s: to identify newborns at risk for selected disorders in the presymptomatic phase/early stages of the disorder, with the hope of preventing disease progression. Although the success of this rationale varies between disorders, this guiding principle has led to the expansion of screening from phenylketonuria (PKU) to over 50 diseases now, and more on the horizon.



Figure 1. Baby's first test. Source: New York Newborn Screening Laboratory.

With screening being conducted for so many disorders, it has become more difficult to synthesize the amount of information needed to understand the full breadth of the program. In this review, we hope to provide a practical guide to the current state of NBS, with particular emphasis on the unique situation of neonates in the NICU. Rather than being exhaustive in detail, useful links for additional information have been included throughout the review.

## HISTORY: THE TIMELINE OF NBS

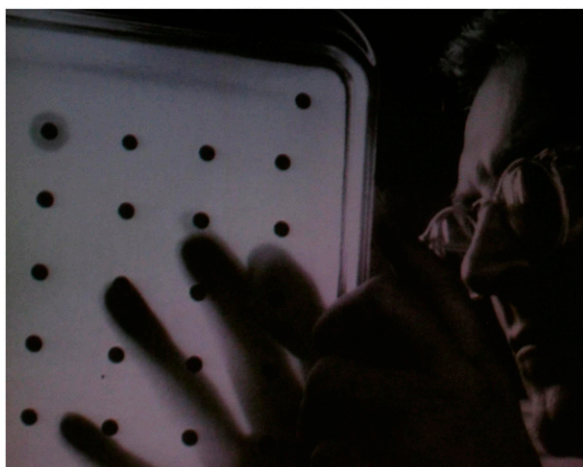
The development of NBS has taken a stepwise approach as discoveries in disease natural history, diagnostics, and therapeutics have led to initiatives in NBS technologies. NBS has been a reality for the early diagnosis of PKU since the early 1960s, and this has served as the paradigm for the expansion of NBS to the present.

The timeline outlined below summarizes the major milestones in NBS in New York State and is summarized in detail at <https://www.wadsworth.org/programs/newborn/screening/history>. This parallels the development in other states, but because NBS is mandated at the state level, not all states screen for the same disorders.

- 1930s: At the Letchworth Village State School, Thiells, NY, George Jarvis identified 50 people with intellectual disabilities as a result of PKU. This follows the work of Asbjorn Folling in Norway who discovered PKU in 1934. (1)
- 1958: Robert Guthrie, a microbiologist-pediatrician at the State University of New York, Buffalo, created an inexpensive method, the bacterial inhibition assay (BIA),

which screened for PKU. The BIA relies on the fact that bacteria grown in a medium that does not contain phenylalanine will show enhanced growth around a blood spot with a high phenylalanine concentration.

- 1960: Robert Guthrie coordinated a 29-state pilot study screening 400,000 newborns for PKU (Fig 2). This proved so successful that many states instituted NBS immediately. This was done by scaling up the BIA to large plates where multiple patients could be tested simultaneously.
- 1965: New York State law for NBS (Public Health Law 2500a) went into effect, mandating that every newborn be screened for PKU.
- 1968: New York State started a pilot screening program for galactosemia and maple syrup urine disease (MSUD).
- 1970s: New York State began screening for sickle cell disease (1975) and congenital hypothyroidism (1979).
- 1989: Biotinidase deficiency was added to NBS.
- 2002: Tandem mass spectroscopy (MS/MS) technology was introduced for the testing of PKU, MSUD, homocystinuria, and medium chain acyl-CoA dehydrogenase (MCAD) deficiency.
- 2002: Newborn screening for cystic fibrosis and congenital adrenal hyperplasia was added to the screening panel.
- 2006: Krabbe disease was added to the screening panel in New York State.
- 2013: Aiden's Law mandated the addition of X-linked adrenoleukodystrophy to the NBS panel.
- 2014: Pompe disease was added to the NBS panel.
- 2018: New York State started screening for mucopolysaccharidosis type I, spinal muscular atrophy (SMA), and gaundinoacetate methyltransferase (GAMT) deficiency.



**Figure 2.** Robert Guthrie holding a bacterial inhibition assay plate to test for phenylketonuria. Used by permission of the Robert Guthrie Foundation.

## THE NEWBORN SCREENING SPECIMEN

The newborn screen filter paper card, also known as the Guthrie card, has been the method used for specimen collection since the introduction of NBS. It has proved to be the most stable method for specimen collection and preservation. Not only can it be used to measure metabolite levels, but it can also be used for enzymatic assays and molecular sequencing. The specimens also have long-term stability and can be reanalyzed at future time points. The absolute longevity has not been determined, because few states preserve specimens. The New York State NBS program has successfully reanalyzed samples that are about 10 years old.

One challenge of NBS is adequate specimen collection. A video demonstrating proper specimen collection technique can be found at: <https://www.youtube.com/watch?v=o6NYIKAgI34&feature=youtu.be>.

Another challenging aspect of NBS is determining the ideal timing of specimen collection. The timing of newborn screening in the nursery is ideally done at 24 to 48 hours after birth. This timing can also be applied to patients in the NICU. In our NICU, we recommend collecting an NBS specimen at entry to the NICU and then at 7 days if the collection was done before 24 hours of age. Samples taken at less than 24 hours of age are inconsistent for the detection of all NBS disorders, and increases the risk of patients being missed. If the patient is transferred from an outside hospital, it is the responsibility of the sending and receiving hospitals to send specimens. Ideally, specimens should be collected just before the next feeding. Patients receiving total parenteral nutrition are more likely to have elevated levels of amino acids.

The rate of abnormal screening results is higher in NICU patients, often because enzyme systems in the preterm neonate are more likely to be immature, and also it is more likely that NICU infants are sick and metabolically unstable. The laboratory values of critically ill neonates can mimic inherited metabolic disorders. For a recovering sick neonate, the metabolic abnormalities resolve, whereas patients with inherited metabolic disorders have persistently abnormal laboratory values.

In the NICU, there are often requests for repeat NBS specimens. Most abnormalities are only mild elevations and usually a repeat specimen yields a normal result, with no need for specialist evaluation. However, if the repeat specimen continues to show abnormal elevations, even if mild, then evaluation by a specialist is required. A sample management algorithm is shown in Fig 3.



Hearing loss and critical congenital cyanotic heart disease are mandated parts of the NBS panel, but are evaluated locally at the birth hospital before discharge.

## TIMELINESS OF NBS RESULTS

One important consideration of the screening process is how quickly the initial results are available. It has been recognized that neonates with certain disorders can exhibit initial symptoms in the first week after birth. In fact, for some disorders, infants can become sick before the results of the screen are available. For an at-risk neonate, the results of the screen can direct a prompt intervention, whereas for a sick neonate, the result may be lifesaving. This has been particularly important in our experience for infants with MSUD and galactosemia, for whom the results of screening lead to lifesaving interventions. For some severe inherited metabolic disorders, patients can deteriorate in the first few days after birth, before NBS specimens are even processed; the 2 most recent neonates with severe citrullinemia in our NICU had severe hyperammonemia at 2 days of age, while the results of their screens only became available after we had diagnosed the patients based on clinical and laboratory findings.

Every part of the time-sensitive screening process has to be optimized. This includes having all specimens collected 24 to 48 hours after birth, making sure that all specimens are sent to the state laboratory the next day, and ensuring that samples are processed on the morning of their arrival and results reported the following day, or that evening for emergencies. With this in mind, the goal is to have all results reported by 5 days after birth for critical conditions and by day 7 for the rest. This has been summarized by the Federal Advisory Committee on Heritable Disorders in Newborns and Children (<https://www.hrsa.gov/advisory-committees/heritable-disorders/>

[newborn-screening-timeliness.html](https://www.hrsa.gov/advisory-committees/heritable-disorders/newborn-screening-timeliness.html)). If clinicians have a high suspicion for an inherited metabolic disorder while waiting for the NBS results, the neonate should be tested for hyperammonemia, hypoglycemia, and metabolic acidosis.

The referral center that evaluates the NBS-positive cases also has to ensure that patients are evaluated as quickly as possible. As soon as our center receives a referral from the state, we aim to contact the family within a couple of hours and evaluate the newborn within a few hours if the results are critical. When our clinicians call the family to discuss the referral, we determine the infant's severity of illness. If there is evidence of illness we arrange to see the patient in the emergency department, in case admission is necessary. If the patient is stable and cannot be seen the same day, we will often arrange for the patient to be seen by the pediatric clinician first, and then we will see the patient the following day. This situation occurs when the results are only mildly outside the normal range, with low expectation of a true case, but when the screened disorder itself could be critical.

A report from the Government Accountability Office provides a detailed account of the current status of NBS timeliness and strategies to improve timely reporting (<https://www.gao.gov/assets/690/681635.pdf>).

## TEST SENSITIVITY AND SPECIFICITY

One of the key components of any screening process is the sensitivity and specificity of each test, as well as the positive predictive values of the test. Sensitivity represents the chance that the test will correctly identify an infant who has the disease (true-positives/true-positives + false-negatives), whereas specificity represents the chance that the test will correctly identify an infant who does not have the disease (true-negatives/true-negatives + false-positives). As the

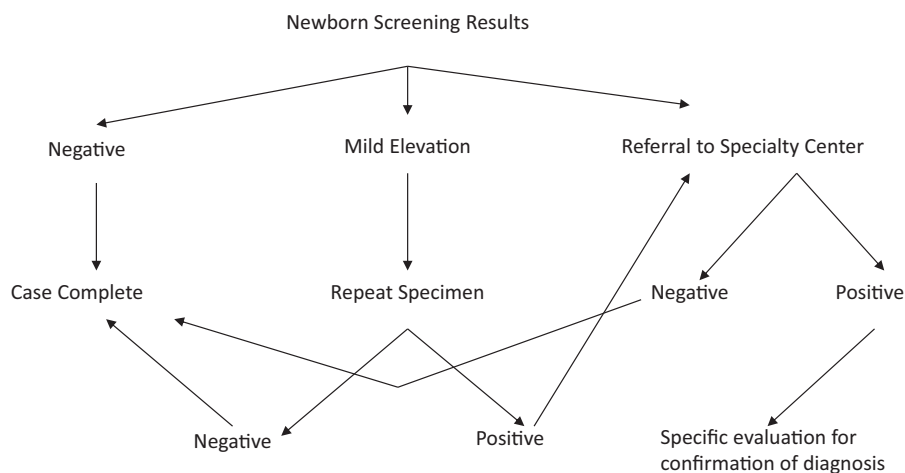


Figure 3. Algorithm for management of newborn screening referrals.

sensitivity increases, the specificity decreases and the false-positive rate increases. To achieve the goal of an almost zero false-negative rate, the false-positive results will increase with a corresponding decrease in the positive predictive value of the test result. In the real world, if a test has a high false-positive rate then needless follow-up testing is conducted on patients without disease. This has a negative impact on the patient, the family, and the system. If a screen has a positive predictive value of 10%, then 10 patients require follow-up testing before 1 patient with the disease is diagnosed. The positive predictive value (true-positives/true-positives + false-positives) varies somewhat for each disorder on the screening panel, and is largely dependent on where the cutoff values are set by the state testing laboratory. These concepts are shown graphically in Fig 4.

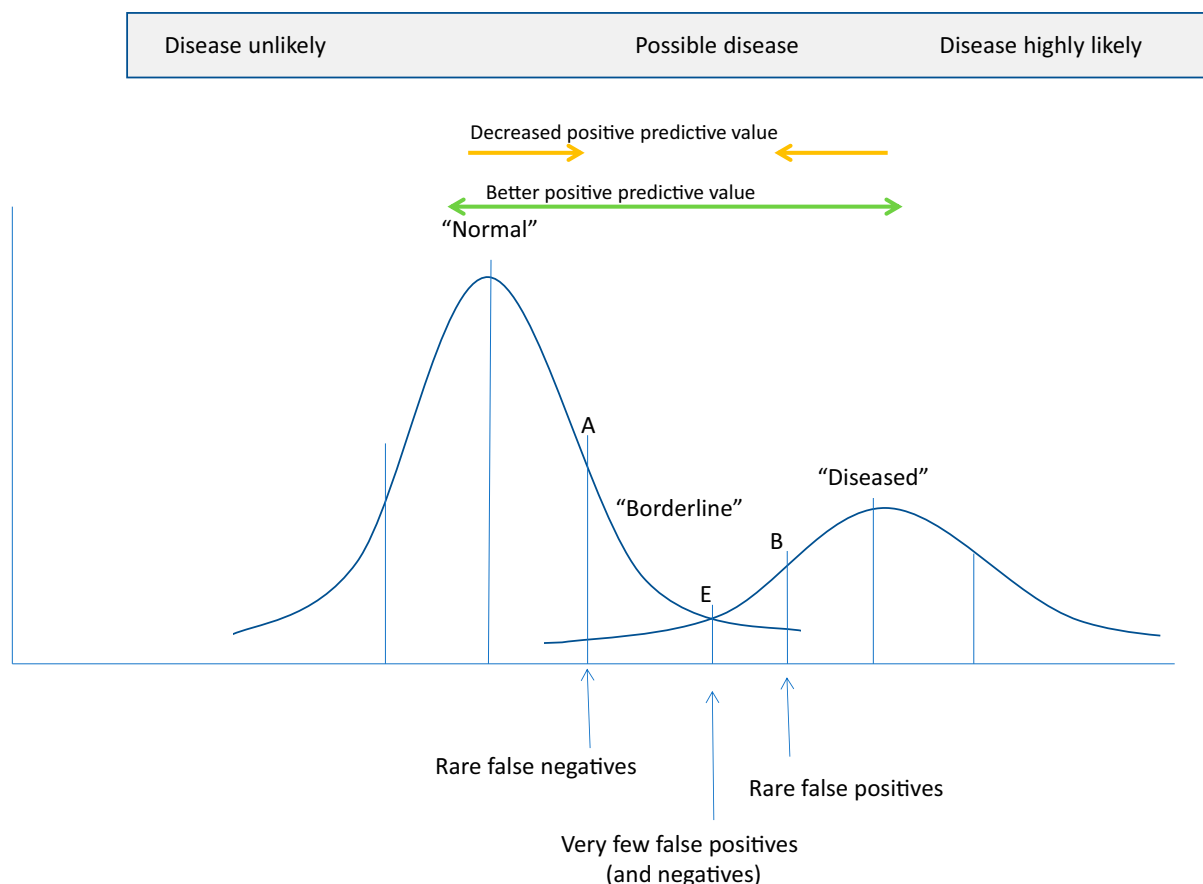
The refinement of cutoff values and use of secondary testing procedures for screen-positive patients has helped decrease the overall level of false-positive results, but false-positive cases still outnumber true cases by a wide margin. In New York State, positive results are tiered, with mild elevations only requiring a repeat screen whereas higher

elevations are actionable and require the patients to be seen by the responsible specialist.

Some disorders have a higher level of false-positive results, and others have a good separation between unaffected and affected individuals, such that the positive predictive value for an elevated level is close to 100%. This latter scenario is found in testing for very-long-chain fatty acid levels (ie, X-linked adrenoleukodystrophy), in which there is good separation between normal and abnormal values. The use of molecular analysis in screening can cloud the diagnosis, because the detection of *variants of unknown significance* can delay resolution of cases. (2)

## NBS DISORDERS

The number of disorders screened varies among states. Most disorders listed on the recommended uniform screen panel (RUSP) have been adopted by most states (Fig 5). However, differences may occur when new disorders are added to the RUSP, and each state requires a different amount of time to obtain funding and legislation to add



**Figure 4.** Cutoff bimodal values of negative and positive results. This figure demonstrates the screening values for all patients with and without disease. Where the curves overlap and the point where the cutoff value is set determines the number of false-positive cases that may be uncovered. It also determines the risk of missing a true case, the false-negatives. The separation of the curves is critical to the positive predictive value of the test.

Core Condition	Metabolic Disorder			Endocrine Disorder	Hemoglobin Disorder	Other Disorder
	Organic acid condition	Fatty acid oxidation disorder	Amino acid disorder			
Propionic Acidemia	X					
Methylmalonic Acidemia (methylmalonyl-CoA mutase)	X					
Methylmalonic Acidemia (Cobalamin disorders)	X					
Isovaleric Acidemia	X					
3-Methylcrotonyl-CoA Carboxylase Deficiency	X					
3-Hydroxy-3-Methylglutaric Aciduria	X					
Holocarboxylase Synthase Deficiency	X					
β-Ketothiolase Deficiency	X					
Glutaric Acidemia Type I	X					
Carnitine Uptake Defect/Carnitine Transport Defect		X				
Medium-chain Acyl-CoA Dehydrogenase Deficiency		X				
Very Long-chain Acyl-CoA Dehydrogenase Deficiency		X				
Long-chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency		X				
Trifunctional Protein Deficiency		X				
Argininosuccinic Aciduria			X			
Citrullinemia, Type I			X			
Maple Syrup Urine Disease			X			
Homocystinuria			X			
Classic Phenylketonuria			X			
Tyrosinemia, Type I			X			
Primary Congenital Hypothyroidism				X		
Congenital adrenal hyperplasia				X		
S,S Disease (Sickle Cell Anemia)					X	
S, βeta-Thalassemia					X	
S,C Disease					X	
Biotinidase Deficiency						X
Critical Congenital Heart Disease						X
Cystic Fibrosis						X
Classic Galactosemia						X
Glycogen Storage Disease Type II (Pompe)						X
Hearing Loss						X
Severe Combined Immunodeficiencies						X
Mucopolysaccharidosis Type 1						X
X-linked Adrenoleukodystrophy						X
Spinal Muscular Atrophy due to homozygous deletion of exon 7 in SMN1						X

Figure 5. Conditions listed on the recommended uniform screen panel (RUSP). (Source: Health Resources and Services Administration. Available at: <https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/rusp-uniform-screening-panel.pdf>. Accessed February 21, 2019).

Secondary Condition	Metabolic Disorder			Hemoglobin Disorder	Other Disorder
	Organic acid condition	Fatty acid oxidation disorders	Amino acid disorders		
Methylmalonic acidemia with homocystinuria	X				
Malonic acidemia	X				
Isobutyrylglycinuria	X				
2-Methylbutyrylglycinuria	X				
3-Methylglutaconic aciduria	X				
2-Methyl-3-hydroxybutyric aciduria	X				
Short-chain acyl-CoA dehydrogenase deficiency		X			
Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency		X			
Glutaric acidemia type II		X			
Medium-chain ketoacyl-CoA thiolase deficiency		X			
2,4 Dienoyl-CoA reductase deficiency		X			
Carnitine palmitoyltransferase type I deficiency		X			
Carnitine palmitoyltransferase type II deficiency		X			
Carnitine acylcarnitine translocase deficiency		X			
Argininemia			X		
Citrullinemia, type II			X		
Hypermethioninemia			X		
Benign hyperphenylalaninemia			X		
Biopterin defect in cofactor biosynthesis			X		
Biopterin defect in cofactor regeneration			X		
Tyrosinemia, type II			X		
Tyrosinemia, type III			X		
Various other hemoglobinopathies				X	
Galactosepimerase deficiency					X
Galactokinase deficiency					X
T-cell related lymphocyte deficiencies					X

1. Selection of conditions based upon "Newborn Screening: Towards a Uniform Screening Panel and System." *Genetic Med.* 2006; 8(5) Suppl: S12-S252" as authored by the American College of Medical Genetics (ACMG) and commissioned by the Health Resources and Services Administration (HRSA).
2. Disorders that can be detected in the differential diagnosis of a core disorder.  
Nomenclature for Conditions based upon "Naming and Counting Disorders (Conditions) Included in Newborn Screening Panels." *Pediatrics.* 2006; 117 (5) Suppl: S308-S314.

Figure 5. (Continued).

the disorder to its panel. The implementation of testing for new disorders at the state level varies, and often requires a new law. Also screening for some disorders does not appear on the RUSP, which particular states have taken the initiative to perform. For example, Krabbe disease was added to the NBS screening in New York State in 2006 even though it is not listed on the RUSP.

The disorders listed on the RUSP are classified into core and secondary conditions. The core conditions are

the primary screened conditions, whereas the secondary conditions are detected as a consequence of primary screening. This distinction is made because in most disorders, screening is conducted for the presence of a marker molecule or metabolite, and though the presence of this marker most likely indicates the primary condition, it may also indicate a secondary disorder. So, for instance, elevations in phenylalanine most likely indicate PKU/hyperphenylalaninemia, they may indicate a secondary defect in biopterin metabolism.

In another example, an elevation in tyrosine may indicate tyrosinemia type I, but may also indicate a secondary condition such as tyrosinemia type II or III. Even the more recent addition of X-linked adrenoleukodystrophy (screened positive based on an elevation in the very-long-chain fatty acid C26:1) may secondarily indicate a peroxisomal biogenesis disorder.

Over the years, our medical center has cared for patients with nearly all the core conditions listed on the RUSP. The most common positive diagnosis at our Inherited Metabolic Disease Center remains PKU/hyperphenylalaninemia, but we have observed several (>3 each) cases of methylmalonic acidemia, carnitine uptake defect, MCAD deficiency, very-long-chain acyl-CoA dehydrogenase deficiency, citrullinemia type I, biotinidase deficiency, classic galactosemia, Pompe disease, and X-linked adrenoleukodystrophy.

In general, secondary disorders are rare and less well described. In our experience, the only secondary disorder we have seen with any frequency is short-chain acyl-CoA dehydrogenase (SCAD) deficiency. All patients with this disorder whom we follow have been clinically stable, and it is debated whether this should even be part of the NBS panel at all. (3) We have also seen patients with carnitine palmitoyl transferase type I and II, argininemia, biotinidase deficiency, and tyrosinemia II and III. We have uncovered cases of NICU patients with DiGeorge syndrome as a result of screening positive for a T-cell-related lymphocyte deficiency.

The largest number of disorders listed on the RUSP is metabolic disorders, which are classified into organic acidemias, fatty acid oxidation disorders, amino acid disorders, and others. However, the endocrine disorders (congenital adrenal hyperplasia and congenital hypothyroidism) and hemoglobin disorders (sickle cell disease and other hemoglobinopathies) form the largest number of confirmed diagnoses. New York State produces a yearly report that highlights the number of referrals and confirmed cases (<https://www.wadsworth.org/sites/default/files/WebDoc/1312181853/2017%20Annual.pdf>).

Information about specific disorders is available on many websites. In our clinical practice, we use *GeneReviews* (<https://www.ncbi.nlm.nih.gov/books/NBK1116/>) to seek information on the specific disorders, and the American College of Medical Genetics and Genomics (ACMG) ACT Sheets ([http://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT\\_Sheets\\_and\\_Algorithms.aspx](http://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx)) for information about the initial evaluation for the specific abnormal screen. The Baby's First Test website has a link to outline the disorders tested in each state (<https://www.babysfirsttest.org>). The current RUSP can be found on the

ACMG website (<https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html>).

## EXPERIENCE WITH NEWBORN SCREENING IN THE NICU

Follow-up of abnormal NBS results is a critical element of neonatal management in the NICU. The procedures for specimen collection and follow-up should be closely aligned. A patient's NBS result will frequently be available before discharge, and it is imperative that a system is in place to monitor the efficiency of the process, to make sure that repeat samples are sent promptly, and that open cases are followed closely to completion.

Because neonatal patients are frequently metabolically compromised as a result of their clinical status and prematurity, it is common for NICU samples to be mildly abnormal, and repeat specimens often need to be sent. It is also more common for results of NICU patients to be actionable (ie, the responsible specialist is consulted to formally evaluate the patient). The Utah Newborn Screening Program has produced a useful document on NBS for sick or premature newborns (<http://health.utah.gov/newborn-screening/PDF/SupportProcScreeningSickPreterm.pdf>).

## OUR EXPERIENCE WITH NEWBORN SCREENING IN THE NICU SETTING

In our NICU, we often get referred formally and for curbside consultation about the results of a patient's NBS result. Most frequently, the results are only mildly out of range and repeat analysis is normal, and the case is closed. Occasionally, the repeat specimen is abnormal and a more formal evaluation is needed. In the NICU setting, low carnitine levels have been among the more common reasons for referral. This is particularly the case for patients receiving prolonged total parenteral nutrition, because our NICU does not supplement the total parenteral nutrition with L-carnitine. Invariably, these cases resolve over time as the diet normalizes, though there have been a few cases in which the levels were low as a result of maternal carnitine uptake deficiency. The most common situation is when the initial newborn screen carnitine level is normal, but at repeat NBS at 4 weeks of age, the level is abnormal, thus pointing to an acquired disorder. Repeat screening in NICU patients can lead to situations in which a different abnormality can be seen on each test; often these are only fully resolved when the infant is metabolically stable and tolerating full oral feedings.

In the NICU, we have also made several diagnoses as a consequence of an abnormal NBS result. Sometimes, this

occurs in a patient who is already showing signs of the disorder. As mentioned previously, 2 patients with citrullinemia presented in the NICU with hyperammonemia, requiring prompt intervention. In both cases, the results of NBS were reported after we had confirmed the diagnosis clinically. A patient may present with metabolic decompensation before the results of the screen are available; this is an important point and applies to many of the most severe inherited metabolic disorders. Most recently, a newborn who underwent screening was referred with a possible organic acidemia; unfortunately, the patient had severe decompensation by the time of arrival in the NICU. Fortunately, we were able to diagnose methylmalonic acidemia based on a molecular analysis; this will be important for the family for future family planning.

Recently, we diagnosed a female infant born at 26 weeks' gestation with Pompe disease based on an abnormal screening result. On initial evaluation, she appeared to have late-onset Pompe disease, but over time, the patient developed cardiomyopathy; a repeat enzyme assay performed at 1 month of age revealed enzyme activity more clearly in the infantile-onset Pompe disease range. This case revealed that patients with abnormal newborn screening results consistent with Pompe disease can have an atypical presentation of infantile-onset Pompe disease, such that not all present with cardiomyopathy at birth. This has been demonstrated to be true in other patients we have diagnosed with Pompe disease on the basis of an abnormal screening result.

Immaturity of enzyme systems in the premature neonate can uncover potentially mild or asymptomatic disorders. This is a situation we have noted several times. New York State does not typically screen patients who are positive for the Duarte variant (mild) galactosemia, but we have identified such patients based on the comorbidities of indirect hyperbilirubinemia and abnormal liver function tests. In this situation, the patients' conditions may have affected the activity of the galactose-1-phosphate uridylyltransferase activity.

## MANAGEMENT OF NEWBORN SCREENING REFERRALS IN NEW YORK

In New York, programs that have specific experience in the management of a disorder listed on the screening panel can apply to the New York State Newborn Screening Program to be a designated referral center for the program. This designation is dependent on the facility having trained physicians to evaluate and manage a patient referral. This includes not only specialty medical care, but the ability to complete the necessary testing, initial management, and

development of a management plan for the newly diagnosed patient. As the number of disorders has expanded, the number of specialists involved with directly managing patient referrals has increased; sometimes, more than 1 specialty may be involved. The largest number of disorders is referred directly to specialists in inherited metabolic disorders. Other specialists include cardiology (Pompe disease, critical congenital cyanotic heart disease, and some fatty acid oxidation disorders), otolaryngology (hearing loss), endocrinology (congenital hypothyroidism and congenital adrenal hyperplasia), hematology (sickle cell disease, hemoglobinopathies), immunology (severe combined immunodeficiency), and neurology (spinal muscular atrophy).

The referral center communicates with the State Newborn Screening Laboratory about the disposition of the patient referral, whether the diagnostic evaluation was positive or negative, and the specific details of the patient's test results. The correlation between the screening result and the outcome of the patient evaluation is critically important for the ongoing process of improving screening. This includes decisions on where the cutoff levels are set for each disorder. New disorders added to the panel tend to have slightly lower cutoffs, in order to not miss a case. This was true in New York for MCAD deficiency, where a high proportion of the initial referrals tested negative on follow-up. These results were reevaluated by the state laboratory and the cutoffs have since been raised, resulting in fewer critical referrals and a higher positive predictive value for the newborn screen result. (2)

## ADDING DISORDERS TO THE NBS PANEL

The expansion of NBS has been based on several factors, but most importantly, it has been determined by the development of therapies for otherwise devastating disorders, and new technologies to detect and screen for them. The first major expansion of NBS occurred in 2002 with the incorporation of MS/MS technology into the New York State NBS. For the first time, it was possible to test for many disorders simultaneously. In most states, this increased the number of disorders screened for from about 10 to more than 40. MS/MS allows for multiplexing of the screening process with 1 test simultaneously measuring the levels of many metabolites or the enzyme activity of many disorders. Before the introduction of MS/MS, each screened disease had 1 specific test. Although it required large capitalization to set up MS/MS at state NBS laboratories, the incremental cost of adding another disorder to the screening panel was not excessive, as long as the same technology could be used to screen for the disorder.



With the advent of MS/MS, however, early problems arose with the large number of false-positive results and the high number of samples that required repeating. It also became apparent over time that certain metabolic disorders were being identified more commonly than previously had been diagnosed clinically. This included many newly diagnosed patients with SCAD deficiency and 3-methyl crotonyl carboxylase deficiency; however, nearly all of these patients have been clinically asymptomatic. One of the unintended consequences of NBS is that this new technology has medicalized some patients who would not have been diagnosed before the expansion of NBS.

Since the initial expansion of NBS in the early 2000s, it became apparent that a process needed to be implemented to more carefully consider which disorders should be added to the screening panel. There was increasing concern that some of the disorders did not meet the criteria for screening. (4) To address this concern, a formal process has been set in place to determine which disorders are suitable to be added to the RUSP. This was confirmed by the Newborn Screening Saves Lives Act of 2007 (<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/about/newbornscreeningsaveslives.pdf>) and led to the establishment of the Advisory Committee on Heritable Disorders in Newborns and Children. One of the roles of this committee is to evaluate conditions nominated for addition to the RUSP. A formal nomination form has to be submitted to the committee for scientific review. (<https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/Nominate-condition/nomination-form.pdf>). A detailed description of the disorder is required with an explanation about the suitability, benefits, and methods of screening as well as the response to therapeutic interventions. Often a condition will be rejected if there is insufficient evidence of the benefits of screening. The Association of Public Health Laboratories has a useful document that describes the approach to adding disorders to the RUSP ([https://www.aphl.org/aboutAPHL/publications/Documents/NBS\\_MN\\_NBSPanelConditions\\_FactSheet\\_102015.pdf](https://www.aphl.org/aboutAPHL/publications/Documents/NBS_MN_NBSPanelConditions_FactSheet_102015.pdf)). A history of the steps that have been taken to approve the tests that are currently on the NBS is summarized at <https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/previous-nominations/summary-of-nominated-conditions-to-RUSP-508c.pdf>.

## RECENT ADDITIONS TO THE NEWBORN SCREEN

NBS continues to expand as developments in technology lead to new treatments for previously untreatable disorders. For many disorders, these new therapeutic options have the

best outcome if initiated in the presymptomatic phase of the disorder; therefore, early screening of these disorders becomes imperative.

### Pompe Disease (Added to RSUP March 2015)

Pompe disease is a muscle lysosomal storage disorder with a spectrum of clinical findings depending on the level of residual activity of the lysosomal acid  $\alpha$ -glucosidase enzyme. (5) The most severe presentation is infantile-onset Pompe disease; affected patients have cardiomyopathy at birth with worsening muscle weakness and respiratory distress in the first few months of age. Untreated, these patients rarely survive beyond 1 year of age. A pilot study conducted in Taiwan showed the benefit of early treatment with recombinant  $\alpha$ -glucosidase in patients diagnosed with NBS compared with patients diagnosed clinically. (6) NBS for Pompe disease also detects patients with late-onset Pompe disease, which generally refers to patients diagnosed after the first year of age with slowly progressive disease. However, often these patients only become symptomatic in adulthood and so there is a long latency between screening and the need for therapeutic intervention. (6)(7)

### X-Linked Adrenoleukodystrophy (Added to RUSP February 2016)

X-linked adrenoleukodystrophy is a peroxisomal disorder that predominantly affects boys in childhood, with the peak age at presentation being 3 to 8 years. (8) The disorder presents with progressive white matter disease (leukodystrophy) that has been well characterized. Patients previously had been clinically diagnosed with evidence of severe leukodystrophy already present. With NBS, patients are diagnosed when the earliest changes in white matter are detected, before the onset of clinical disease. At this stage, patients are most amenable to therapeutic intervention with bone marrow transplantation, or more recently, gene therapy, which prevents progression of the most severe cerebral form of the disease.

### Spinal Muscular Atrophy (Added to RUSP July 2018)

Spinal muscular atrophy (SMA) is the second most common autosomal recessive inherited disorder, after cystic fibrosis, in the white population (also on the NBS panel). (9) Most commonly, it presents with the infantile form SMA type I, with severe muscle weakness and respiratory distress in the neonate. Most patients become ventilator dependent in the first year of age, with a guarded long-term prognosis. In December 2016, the US Food and Drug Administration approved nusinersen, the first drug approved to treat children (including newborns) and adults

with SMA. (10) Nusinersen treats patients with SMA who have deletions in chromosome 5q leading to a deficiency in the SMN1 protein.

#### Mucopolysaccharidosis Type 1 (Added to RUSP February 2016)

Mucopolysaccharidosis type 1 is a lysosomal storage disorder caused by the deficiency of lysosomal enzyme iduronidate sulfatase. (11) This disorder has a wide spectrum of presentations, ranging from Hurler syndrome on the severe end, with early-onset and central nervous system involvement, to the attenuated Schie syndrome that presents later and generally without central nervous system disease. Severe patients are amenable to bone marrow transplantation, whereas milder attenuated patients may respond well to enzyme replacement therapy.

#### Guanidinoacetate Methyltransferase Deficiency (Pending addition to RUSP)

Guanidinoacetate methyltransferase (GAMT) deficiency is an autosomal recessive disorder that alters creatine metabolism. (12) Affected patients have abnormalities in their nervous system and muscles. (12) (In October 2018, New York State added GAMT deficiency, mucopolysaccharidosis type 1, and SMA to the NBS panel.)

### THE FUTURE

As new treatments for previously untreatable disorders become a reality, it is imperative to develop a screening method for these disorders, because it is most likely that patients will be responsive to new therapeutic interventions if started early in the course of the disease and before signs of severe morbidity become apparent. In the past 2 decades, molecular technology has had a greater role in the NBS process and this is likely to continue. Many disorders for which metabolic markers or enzymatic testing are not available may be amenable to molecular screening in the future.

### CONCLUSIONS AND CONCERNS

NBS is the largest public health initiative in the country. Since the early 1960s, over 200 million newborns have been screened in the United States. NBS has expanded exponentially, from screening only for PKU to now screening for nearly 60 disorders in many states. The demands of screening continue to grow with the need for follow-up and management of an ever-increasing group of disorders. The manpower to manage the conditions of these newly diagnosed patients is becoming a concern, because with

increasing complexity of treatment, the expense also increases. Although each state mandates screening, no such mandate exists to cover the cost of follow-up testing and treatment—the so-called “unfunded mandate.” Although rare diseases formed a small proportion of medical care in the 1960s when very few treatments existed, now with the availability of increasingly complex and expensive treatments, insurance companies are more and more aware of these growing expenses.

As with most new technology, advances fail to keep up with the ethical, legal, social, and insurance implications of the process. How do we as a society decide the limits of this technology, what disorders should be screened, or whether insurance companies will dictate who can be treated? These questions remain unanswered but need to be discussed and addressed in the years to come.

### USEFUL WEBSITES

- ACMG ACT Sheets  
[http://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT\\_Sheets\\_and\\_Algorithms.aspx](http://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx)
- The Recommended Uniform Screen Panel  
<https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html>
- How to Nominate a Condition to the RUSP  
<https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/nominate.html>
- Baby's First Test  
<https://www.babysfirsttest.org>
- Newborn Screening of Sick or Preterm Newborns  
<http://health.utah.gov/newbornscreening/PDF/Support-ProcScreeningSickPreterm.pdf>

### American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the indications, limitations, and techniques for newborn screening for genetic disorders
- Recognize the controversies associated with the introduction of new genetic tests for rare and common diseases that present in the neonatal period
- Understand factors that affect the rationale for screening for a condition or disease (eg, prevalence, test accuracy, risk-benefit, disease burden, presence of a presymptomatic state)
- Calculate and interpret sensitivity and specificity
- Calculate and interpret positive and negative predictive values

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## Navigating Newborn Screening in the NICU: A User's Guide

David Kronn

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# Index of Suspicion in the Nursery

## 1 Dome-Shaped Papules and Nodules in Monozygotic Twins

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### PRESENTATION

A pair of male monozygotic twins is born at 38 weeks of gestation via a cesarean delivery to a 29-year-old woman with normal prenatal care. Three ultrasound scans are obtained during pregnancy, confirming monochorionic-monoamniotic twin gestation from the first study, and the presence of an amniotic band that does not affect any product in the second ultrasound scan. The rest of the perinatal history is unremarkable.

Since the first week after birth their mother has noticed small lesions on the face and trunk. They are seen in the hospital at 15 days of age. On physical examination, they have yellowish-brown, soft dome-shaped papules and nodules, 0.5 to 2 cm in diameter, affecting the head, trunk, and extremities. Twin number 1 has 21 lesions and twin number 2 has 25 (Figs 1 and 2). They are asymptomatic, neither twin has hepatosplenomegaly or enlarged lymph nodes, and neither their parents nor grandparents have similar skin lesions.

A biopsy of one of the lesions shows a massive dermal infiltrate of round, medium-sized mononuclear cells with abundant cytoplasm and reniform nuclei that extended to the subcutaneous tissue (Fig 3A). Immunohistochemistry was positive for CD68 (Fig 3B), CD33, and CD163; and negative for CD1a, compatible with non-Langerhans cell histiocytosis (LCH) phenotype. Results of abdominal ultrasonography, complete blood cell count, and ophthalmologic assessment were all reported normal in both children. Viral load for cytomegalovirus and Epstein-Barr virus were negative.

Laboratory tests in both twins, combined with the biopsy and examination findings, confirm the diagnosis.

### DISCUSSION

Juvenile xanthogranuloma (JXG) is the most common non-LCH. (1)(2) The non-Langerhans cell histiocytosis (non-LCH) phenotype includes a group of disorders defined by the accumulation of histiocytes that do not meet the phenotypic criteria for the diagnosis of Langerhans cells. (1)(3)

JXG mainly affects children younger than 2 years and is characterized by single (67%) or multiple reddish-yellow papules predominantly located on the head and neck (42%) followed by the trunk (26%) and lower (16%) and upper extremities (15%), (4) and, rarely, in other organs. This lesion tends to spontaneously regress. (5)(6) The term “xanthogranuloma” refers to the histologic findings of lipid-laden histiocytes with a vacuolated, foamy xanthomatous cytoplasm and giant cells. (6)

**AUTHOR DISCLOSURE** Drs Campos-Cabrera, Morán-Villaseñor, and Pasquel-García have disclosed no financial relationships relevant to this article. Dr García-Romero has disclosed that she receives speaker honoraria from Pierre Fabre Mexico and IFC Cantabria. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





**Figure 1.** Multiple yellow-red nodular lesions in the head, limbs, and trunk of both twins.

JXG affects all races, with a slight male predominance (1.5:1). (6) The incidence is not established. Its pathogenesis is unknown, but there are theories regarding a reactive histiocytic response to a physical or infectious stimulus, (2) such as varicella and cytomegalovirus, (7)(8) or a genetic predisposition. (3)(5)(9)

In 5% to 17% of cases, lesions may appear soon after birth and in 40% to 70% of patients, during the first year of age. (2)(6) The lesions of JXG present as well-demarcated reddish papules or nodules varying from 0.5 to 2.0 cm in diameter, with giant lesions (up to 10 cm); these papules eventually become yellowish plaques or macules as they involute spontaneously. (3)(5) Multiple cutaneous lesions, like those seen in the current patients, are seen in approximately 5% to 7% of patients. (4)(10)

Systemic involvement occurs in 5% of patients, (8) most frequently the eyes (0.3%–0.5% of patients with JXG), (6) but the liver, oropharynx, lungs, spleen, muscle, heart, kidneys, retroperitoneum, and central nervous system can also be affected, with clinical manifestations including obstructive jaundice, liver dysfunction, coagulopathy, hypersplenism, and bicytopenia. (5)



**Figure 2.** Dome-shaped yellowish plump nodules.

The risk for ocular involvement is highest in children younger than 2 years with multiple skin lesions (>3 lesions) and the micronodular form of JXG (lesions ≤10 mm in contrast to the macronodular >10 mm). (4) Most ocular JXGs occur on the iris, followed by the eyelid and orbit. (4) (6) Orbital involvement is rare and occurs in the perinatal period with unilateral exophthalmos. (6) Other clinical data include a spontaneous hyphema because JXG is the most frequent cause of spontaneous hyphema in children. Unlike cutaneous lesions, intraocular JXGs do not resolve spontaneously and may result in severe secondary glaucoma and vision loss. (4)

Disseminated JXGs have been associated with neurofibromatosis type I, epilepsy, Niemann-Pick disease, urticaria pigmentosa, and juvenile myelomonocytic leukemia. (5)(11) Children with neurofibromatosis type I and JXG have been estimated to have a 20- to 32-fold higher risk for juvenile chronic myelogenous leukemia. (4)(6)

The diagnosis of disseminated JXG is clinical; however, it may be difficult to clinically distinguish it from nodular LCH; therefore, a skin biopsy is recommended. (6)(12) Other differential diagnostic considerations include mastocytoma, benign cephalic histiocytosis, and xanthoma disseminatum. (6)

Histologic examination revealed an accumulation of histiocytes intermingled with Touton-type giant cells and foam cells, and a variable number of eosinophils and lymphocytes; in early lesions, Touton cells can be absent, similar to our patients. (2) These cells are characteristic of xanthomatous lesions, are seen as large multinucleated cells with a ring of nuclei surrounded by foamy (lipids) cytoplasm, and are formed by the fusion of macrophages. (2)(6)

Immunohistochemical staining is negative for S100 and CD1a (both markers of Langerhans cells) and positive for CD68, CD163, CD14, vimentin, and (variably) factor XIIIa. (1)(5)(10)

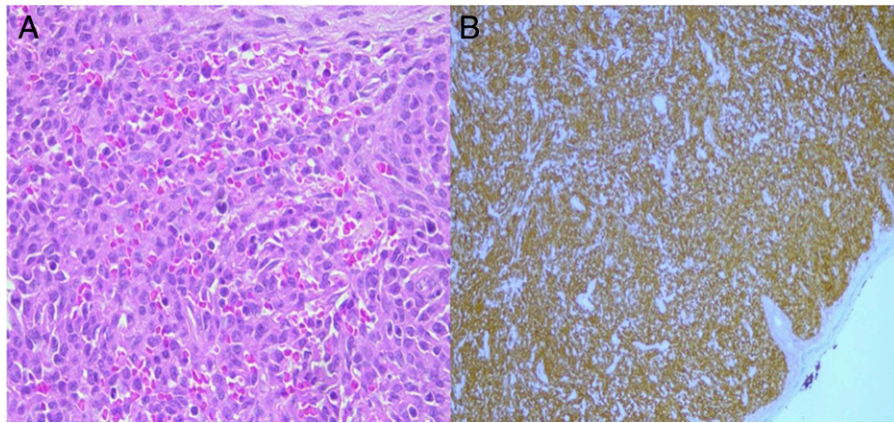
The prognosis in patients without systemic involvement is favorable, with most cutaneous lesions spontaneously regressing without any therapeutic intervention within 6 months to 3 years. (2)

## PATIENT COURSE

With conservative management, the twins' lesions regressed spontaneously over the following months. After 20 months of follow-up, they have not developed new skin lesions or systemic involvement.

## Lessons for the Clinician

- Monozygotic twins have an unusual presentation that supports the hypothesis of a genetic predisposition for a



**Figure 3.** A. Massive histiocytic infiltrate that extends to the subcutaneous tissue (H&E stain, magnification  $\times 40$ ). B. Positive immunohistochemistry for CD68 (magnification  $\times 10$ ).

reactive histiocytic granulomatous response to an unknown stimulus; however, further studies are warranted.

- Disseminated juvenile xanthogranuloma has a benign course and tends to be self-limiting; however, it is necessary to follow up patients to rule out systemic involvement and potential associations with other diseases.
- Skin biopsy is required to help exclude other disorders.
- A complete evaluation is required to determine the presence or absence of extracutaneous involvement.
- Children younger than 2 years and with multiple lesions have a higher risk of ocular involvement, therefore, they must be evaluated by a pediatric ophthalmologist.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the cutaneous and laboratory manifestations, including imaging studies, and management of non-Langerhans cell histiocytoses.

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## Case 1: Dome-Shaped Papules and Nodules in Monozygotic Twins

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# Index of Suspicion in the Nursery

## 2 Seizures, Apnea, Lethargy, and Persistent Hiccups in a Full-Term Newborn

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### PRESENTATION

A female infant weighing 3,265 g is born to a 34-year-old gravida 10, para 8 mother, at 39 5/7 weeks of gestation. The pregnancy is complicated by maternal drug use (cocaine and tetrahydrocannabinol) and inadequately treated group B *Streptococcus* colonization. The infant is delivered via a precipitous vaginal delivery with concerns for placental abruption because of the removal of several large blood clots. At delivery, meconium staining of fluids is noted but the infant is vigorous, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively.

At 14 hours after birth, the infant is first noted to have an episode of right upper extremity twitching, which soon progresses to involve both upper extremities. She also appears hypotonic and lethargic, and is noted to have episodes of apnea, bradycardia, and desaturations requiring continuous positive airway pressure. The infant undergoes a thorough screening for infections and is started on empirical broad-spectrum antibiotics and antiviral coverage (*Herpes simplex*). Serum glucose and electrolyte levels are normal. The infant is then transferred to a tertiary care facility for further care.

On arrival, the infant is noted to be lethargic and hypotonic with shallow breathing. She is also noted to have frequent hiccups. Capillary blood gas is notable for a pH of 7.29, a  $P_{aCO_2}$  of 64 mm Hg (8.5 kPa), and a base deficit of +4. The infant undergoes elective intubation and mechanical ventilation is started. A head computed tomography (CT) scan is obtained and the infant is placed on continuous electroencephalography (EEG) monitoring.

### DISCUSSION

The head CT scan shows slightly diminished gray and white matter differentiation, but is otherwise unremarkable. Because of the infant's clinical presentation, serum ammonia, lactate, pyruvate, uric acid, urine organic acids, serum amino acids, urine reducing substances, and liver and renal function are also tested for metabolic disorders. EEG shows burst suppression pattern with multiple seizures characterized by 1- to 2-Hz poly-spike/sharp waves. The infant is given a loading dose of phenobarbital. Because of persistent seizure activity, she is given another dose of phenobarbital and started on pyridoxine and folinic acid. By day 4, the seizures are well controlled but the infant is noted to have increasingly frequent hiccups with persistent apnea requiring mechanical ventilation. The infant's evaluation for infections is unremarkable. Lumbar puncture (LP) is repeated and cerebrospinal fluid (CSF) is sent for levels of lactate, pyruvate, amino acids, and neurotransmitters along with concomitant repeat serum amino

**AUTHOR DISCLOSURE** Drs Arya and Melton have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



acids. Magnetic resonance imaging (MRI) of the brain with spectroscopy is also performed.

### Differential Diagnosis

The initial presentation of the infant with lethargy, hypotonia, and seizures was concerning for sepsis. But the infant's evaluation for infections was negative. The perinatal history of maternal cocaine use, concern for placental abruption, and meconium staining at delivery also raised concerns for hypoxic-ischemic encephalopathy but the infant had normal examination findings for the first 14 hours after birth and an unremarkable resuscitation. Neonatal drug withdrawal was also a possibility, but the infant did not display any of the other associated symptoms.

A normal CT scan ruled out major structural anomalies and intracranial bleeding, and the MRI did not show signs concerning for a perinatal stroke. Urea cycle defects, organic acidemias, and fatty acid oxidation defects were ruled out because of normal serum glucose, ammonia, lactate and pyruvate, and urine organic acids. Given the persistent apnea and hypotonia, a diagnosis of nonketotic hyperglycinemia (NKH) was suspected.

### The Condition

The MRI revealed symmetric diffusion restriction in the bilateral white matter, internal capsule, brain stem, and cerebellum, raising concerns for an inborn error of metabolism. Magnetic resonance spectroscopy revealed a glycine peak, which was suggestive of NKH. The serum amino acid testing revealed a glycine level of 12.8 mg/dL (1,709  $\mu\text{mol/L}$ ; normal 1.2–5.9 mg/dL [164–791  $\mu\text{mol/L}$ ]), the CSF glycine level was 3.1 mg/dL (418  $\mu\text{mol/L}$ ; normal <0.05 mg/dL [<7  $\mu\text{mol/L}$ ]), and CSF–serum glycine ratio was 0.24, which confirmed the diagnosis of NKH.

NKH, also known as *glycine encephalopathy*, is an autosomal recessive inborn error of glycine metabolism. (1) It is caused by defects in the glycine cleavage system (GCS) which is formed by 4 proteins P, H, T, and L encoded by the *GLDC*, *GCSH*, *AMT*, and *GCSL* genes, respectively. (2) This defect leads to an accumulation of glycine in different body compartments, including the CSF. (3) Glycine serves as both an inhibitory and excitatory neurotransmitter. Its

inhibitory activity in the brainstem and spinal cord is associated with apnea and hiccups, while its excitatory activity at the N-methyl-D-aspartate (NMDA) receptors in the cortex is associated with seizures. (4)

There are 2 types of NKH based on the timing of presentation: classic or neonatal, and atypical. In the classic form, neonates appear normal at birth but progress rapidly within the first few days to lethargy, hypotonia, apnea, and seizures. Persistent hiccups also are usually seen at presentation. (5) After the initial period of ventilator dependency, apnea resolves for most patients in 1 to 3 weeks. (6) Following the neonatal period, severe psychomotor disability is seen in most cases of classic NKH. (5) Congenital brain anomalies like hydrocephalus, retrocerebellar cyst, and abnormalities of the corpus callosum also have been reported with NKH, and their presence confers a poorer prognosis. (7)(8)

Infants with atypical NKH usually have normal development until 6 months of age and then present with 1) mental retardation and seizures (infantile form); 2) episodes of chorea, delirium, and vertical gaze palsies during febrile illnesses (episodic form); and 3) normal intellectual function with spastic diplegia, optic atrophy, and chorioathetosis (late-onset form). (5)(9)

Diagnosis of NKH is made by detecting hyperglycinemia and an elevated glycine level in the CSF with a CSF–plasma glycine ratio typically greater than 0.08. (1) This requires special attention to avoid a traumatic LP and CSF contamination with blood. Mass spectroscopy may also demonstrate a glycine peak, as seen in this case. The diagnosis can also be confirmed by detecting enzyme deficiencies by evaluating the GCS through a liver biopsy or in cultures of lymphoblasts. (10) It is also important to note that organic acidurias and ketoacidosis must be excluded, because inhibition of the GCS in the liver by organic acids can lead to ketotic hyperglycinemia but the CSF–plasma glycine ratio is usually normal. (1) Sodium valproate has also been shown to cause hyperglycinemia by inhibiting the GCS. (11)

### Treatment

Existing therapies decrease seizure frequency and apnea and improve alertness; however, most patients with NKH progress to severe intellectual disability and the overall prognosis

TABLE. Weekly Plasma Glycine Monitoring Results

	NORMAL RANGE	DAY 3	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
Serum glycine	1.2–5.9 mg/dL (164–791 $\mu\text{mol/L}$ )	12.8 mg/dL (1,709 $\mu\text{mol/L}$ )	4.7 mg/dL (627 $\mu\text{mol/L}$ )	1.8 mg/dL (249 $\mu\text{mol/L}$ )	3.7 mg/dL (506 $\mu\text{mol/L}$ )	4.9 mg/dL (653 $\mu\text{mol/L}$ )	5.6 mg/dL (756 $\mu\text{mol/L}$ )



remains poor, despite therapy. (12) Sodium benzoate undergoes conjugation with glycine to form hippurate, which is readily excreted by the kidneys. (13) It can reduce plasma glycine levels to normal but CSF glycine, although reduced, does not return to normal. (12) Dextromethorphan is a noncompetitive NMDA receptor antagonist.

### Progression

Following a multispecialty care conference, the parents in the current case chose to initiate sodium benzoate and dextromethorphan treatment. In the next few days, the infant started showing increasing spontaneous movements and signs of spontaneous breathing, prompting extubation to room air. The infant also started taking partial-volume oral feeds. Plasma glycine levels were repeated weekly and showed an initial downward trend after beginning therapy, but levels started increasing again before discharge (Table). A glycine encephalopathy sequencing panel revealed that the patient was heterozygous for 3 notable missense variants in the *GLDC* gene.

### Lesson for the Clinician

This case shows the importance of suspecting inborn errors of metabolism like NKH for an infant presenting with seizures, apnea, and persistent hiccups.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids.

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## Case 2: Seizures, Apnea, Lethargy, and Persistent Hiccups in a Full-Term Newborn

Shreyas Arya and Kristin Melton

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# Index of Suspicion in the Nursery

## 3 Bradycardia in a Vigorous Newborn

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### PRESENTATION

A female infant is delivered at 38 weeks and 3 days to a 32-year-old gravida 2, para 1 woman via a low transverse cesarean section. At delivery, the neonate is noted to have a spontaneous cry, appropriate respiratory effort, and active movement of all extremities; however, her initial heart rate is noted to be 40 beats/min.

After drying and stimulation, her oxygen saturation on pulse oximetry is noted to remain at 60% at 3 minutes after birth. Blow-by oxygen is started. Despite this intervention, she develops nasal flaring and subcostal retractions. Facial continuous positive airway pressure (CPAP) is initiated with positive end-expiratory pressure of 5 mm Hg and then the infant is transitioned to nasal CPAP. Oxygen concentration is titrated to 100% and oxygen saturations on pulse oximetry increase to greater than 90%. Her work of breathing normalizes. Apgar scores are noted to be 6 and 8 at 1 and 5 minutes, respectively.

Despite effective ventilation and oxygen saturations, the infant's heart rate remains between 40 and 50 beats/min. A 12-lead electrocardiogram is obtained, which confirms the diagnosis (Fig 1).

### DISCUSSION

#### Diagnosis

This infant's presentation was concerning for a cardiac anomaly, given the intractable bradycardia despite adequate respiratory support, and oxygen saturations. Electrocardiographic findings were consistent with complete heart block (congenital atrioventricular block, third degree). She began receiving an isoproterenol infusion starting at 0.15 µg/kg per minute to increase ventricular rate.

On day 1 after birth, isoproterenol was discontinued to obtain baseline hemodynamics and heart rate, which remained at approximately 40 beats/min. Her systolic blood pressures averaged between 60 and 70 mm Hg and her diastolic blood pressures averaged between 25 and 35 mm Hg.

By day 2 after birth, she was transferred to the pediatric cardiac intensive care unit; the pediatric cardiothoracic surgeon carried out a minimally invasive placement of a single right ventricular epicardial bipolar pacing lead and generator using a subxiphoid approach. The pacemaker mode was VVI at a rate of 80 beats/min. Her remaining hospital course was uneventful and she was discharged from the hospital with her family on day 5 after birth.

Maternal and antenatal history was significant for maternal autoimmune arthritis with antibody positivity for anti-SSA/Ro and anti-SSB/La antibodies.

**AUTHOR DISCLOSURE** Drs Timothy, Stetson, Qureshi, Wilkins, and Asay have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

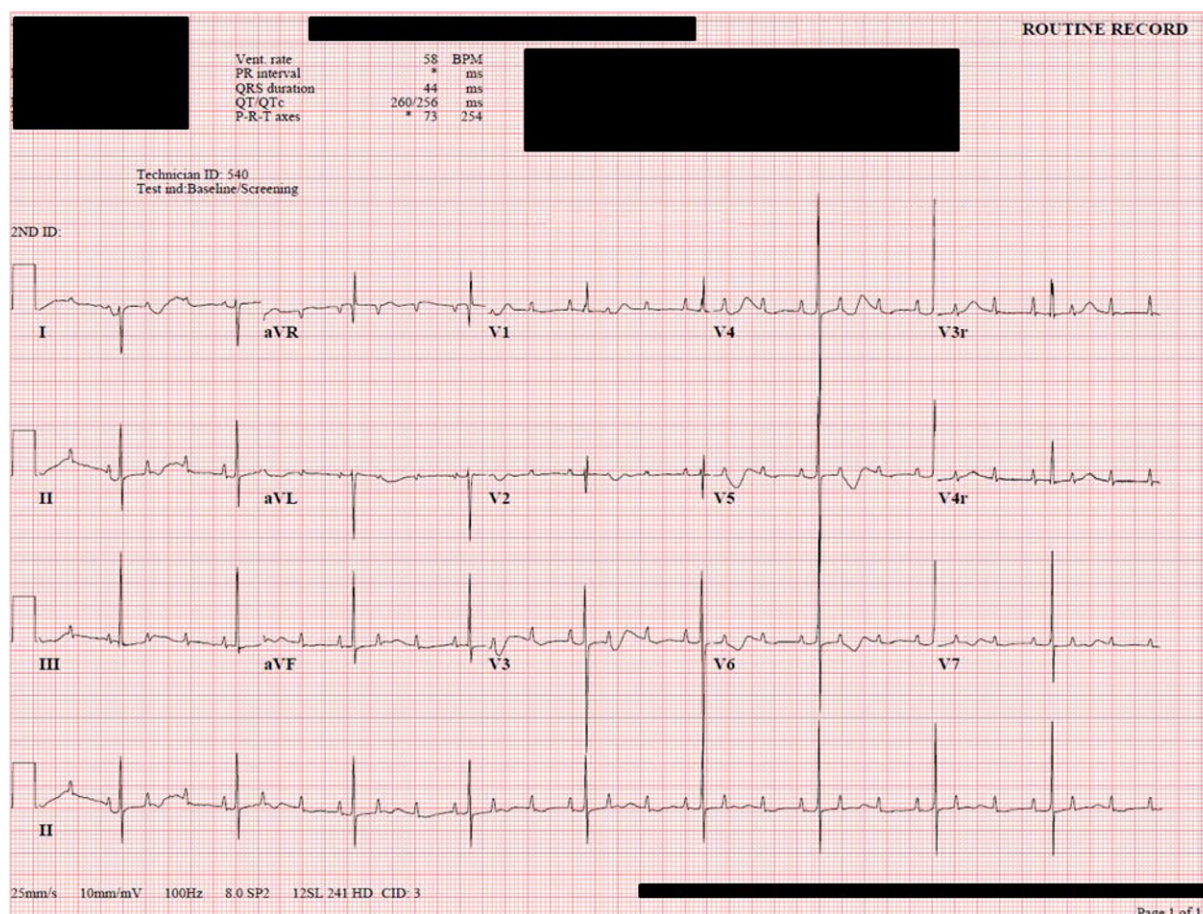


Figure 1. Electrocardiogram of patient obtained on date of birth.

The infant's mother also had been treated with thyroid hormone replacement therapy for hypothyroidism.

In this case, fetal echocardiography performed at 13 weeks of gestation revealed complete heart block (CHB) and large ascites. The mother was started on terbutaline to increase fetal heart rate and dexamethasone to prevent maternal antibody-mediated myocarditis. Serial echocardiography demonstrated CHB at 20, 24, and 28 weeks of gestation with resolution of ascites by 34 weeks of gestation.

### The Condition

Neonatal lupus syndrome is an acquired autoimmune disease that occurs in some infants born to mothers with anti-SSA/Ro and anti-SSB/La antibodies associated with a range of autoimmune disorders, including systemic lupus erythematosus, Sjögren syndrome, idiopathic inflammatory myopathies, systemic sclerosis, mixed connective tissue disease, and rheumatoid arthritis. (1)(2) The condition is characterized by congenital heart block, cardiomyopathy, cutaneous lupus lesions, hepatobiliary disease, thrombocytopenia, or other hematologic cytopenias either independently or concurrently. (3)(4)(5)

The most concerning complication is neonatal CHB, which has a prevalence of about 1% to 2% in infants of anti-SSA/Ro-positive mothers, and a recurrence rate of approximately 17% in subsequent pregnancies. (6) Neonatal lupus accounts for 90% to 95% of CHB cases occurring in utero or during the neonatal period. (4)(7)(8)

Cutaneous features of neonatal lupus, which may be apparent at the time of delivery or after the newborn has been discharged from hospital, include multiple erythematous annular lesions or arcuate macules. The rash is often described as a raccoon-eye appearance, with the face being the most common site affected, followed by the palms, soles, or diaper area (Fig 2). (3)(5)(9)

Anti-SSA/Ro and anti-SSB/La autoantibodies are transplacentally transmitted during the second trimester. (10) It is thought that CHB occurs because of opsonization of anti-SSA/Ro and anti-SSB/La autoantibodies to neonatal cardiocytes in utero, thereby inhibiting these cells from participating in the usual clearance of apoptotic cardiocytes. This results in an accumulation of apoptotic cells, promoting inflammation, remodeling, and fibrosis, which may lead to myocarditis or cardiac rhythm impairment. (10)





**Figure 2.** Photograph of the cutaneous erythematous annular rash of neonatal lupus. (Courtesy of Dr Dawn Davis, Associate Professor of Dermatology and Pediatrics, Mayo Clinic, Rochester, MN.)

Because CHB usually develops between 18 and 24 weeks of gestation, some experts recommend serial fetal echocardiography during this period, with premature atrial contractions and moderate pericardial effusions being concerning for the potential development of CHB. If first- or second-degree heart block is noted on fetal echocardiography, maternal treatment with steroids may prevent progression to CHB. If CHB is detected, treatment with dexamethasone may be initiated to prevent myocarditis, not to treat CHB, because myocarditis is an irreversible complication. (11)(12) The evidence regarding the efficacy of fluorinated steroids in the prevention of mortality in CHB is inconsistent with concerns for adverse effects during pregnancy. (13) In addition, sympathetic  $\beta$ -agonists have been used to increase fetal heart rates in utero, but evidence regarding their impact on mortality is limited. (13)

#### Lessons for the Clinician

- Cardiac anomalies should be considered in the vigorous neonate with bradycardia despite effective ventilation and normal oxygen saturation.
- While the neonatal resuscitation algorithm recommended by the Neonatal Resuscitation Program is the standard of care for resuscitation of newborns, its reliance on heart rate for guidance of interventions limits its usefulness in the resuscitation of infants with congenital heart block.
- Antenatal care for mothers with anti-SSA/Ro and anti-SSB/La autoantibodies should include serial echocardiography by 18 weeks and beyond.
- Evidence suggests that the use of fluorinated corticosteroids such as dexamethasone may protect against the development of congenital heart block, if the treatment is instituted at an earlier stage.

#### ACKNOWLEDGMENT

The authors wish to acknowledge Dr Dawn Davis, Associate Professor of Dermatology and Pediatrics, Mayo Clinic, Rochester, MN, for providing the photograph of the neonatal lupus rash.

### American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how specific fetal diagnoses, such as airway abnormalities, abdominal wall defects, myelomeningocele, or severe hydrocephalus might alter prenatal care and intrapartum management (eg fetal intervention "Exit" strategy)
- Differentiate asphyxia from other causes of depression at birth, including drug effects and hypovolemia
- Understand the significance, limitations, and causes of low Apgar scores, including the relationship between Apgar scores and later outcomes in preterm and full-term infants
- Know the proper approach to airway management in the delivery room
- Know the indications for assisted ventilation, including continuous positive airway pressure, immediately after birth and how to assess its effectiveness
- Know the indications for, techniques, and potential complications of chest compression immediately after birth
- Know the indications, contraindications, and methods of administration of drugs used for neonatal resuscitation
- Know the neonatal developmental cardiac manifestations of maternal diseases and maternal drug and environmental exposures
- Know the appropriate techniques to assess cardiovascular function in the fetus and newborn infant
- Differentiate normal from common abnormal electrocardiographic patterns and rhythms in the fetus and newborn infant
- Know the physiologic consequences of an arrhythmia in a fetus or newborn infant
- Know appropriate management of common arrhythmias in the fetus and newborn infant, and understand the potential complications or adverse effects of approaches and drugs used
- Know the mechanism of action of commonly used adrenergic vasopressor and/or inotropic drugs (eg dopamine, dobutamine, epinephrine)



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## An Extremely Preterm Neonate with Gray Plaques on the Back

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### THE CASE

A 5-day-old preterm male infant presents with gray-brown crusted plaques on the midback with surrounding erythematous patches.

### PRENATAL AND BIRTH HISTORIES

- Born to a 42-year-old gravida 8, para 4-1-2-5 woman.
- Prenatal laboratory findings: Group B *Streptococcus* negative; hepatitis B surface antigen negative; human immunodeficiency virus negative; syphilis IgG antibody negative; *Chlamydia trachomatis* negative; *Neisseria gonorrhoeae* negative.
- Pregnancy complicated by hypertension and maternal use of tobacco and methamphetamines.
- Mother presented with profuse vaginal bleeding. Emergent cesarean delivery performed because of concern for placental abruption and nonreassuring fetal heart rate tracing.
- Estimated gestational age: 24 weeks, 5 days
- Rupture of membranes was at delivery and amniotic fluid was clear.
- Apgar score: 2 and 6 at 1 minute and 5 minutes after birth, respectively.
- Infant resuscitated and underwent intubation in delivery room.
- Birthweight: 800 g (75th percentile); length: 33.8 cm (81st percentile); occipitofrontal circumference: 22.9 cm (63rd percentile).

### PRESENTATION

On admission to the NICU, surfactant was administered and umbilical lines were placed. Ampicillin and gentamicin were started empirically. Over the next 2 days, the infant underwent extubation to noninvasive ventilation, trophic feeds were initiated, and antibiotics were discontinued because the blood culture was negative. Phototherapy was initiated for hyperbilirubinemia. On postnatal day 3, the patient developed acute pulmonary hemorrhage and bilateral grade 3 intraventricular hemorrhage requiring reintubation, blood products, and vasopressor support. Laboratory tests demonstrated hyperglycemia, neutropenia, thrombocytopenia, and elevated C-reactive protein (CRP). Blood culture specimen was obtained and treatment was started with ampicillin and ceftazidime. Bilirubin blanket was added on postnatal day 4 for increasing bilirubin. Antibiotics were discontinued on postnatal day 5 because of negative cultures.

On postnatal day 5, a few gray crusted plaques and surrounding erythema were noted on his midback (Fig 1). The bilirubin blanket was discontinued; treatment

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**Figure 1.** Few gray-brown crusted plaques with surrounding erythema on the back of a premature neonate.

with topical bacitracin was initiated with transient improvement in erythema. On postnatal day 9, the lesions progressed, prompting a dermatology consultation. Bacterial and fungal culture swabs were obtained, and empiric treatment was started with vancomycin, cefepime, and micafungin.

#### Vital Signs (Postnatal Day 9)

- Temperature: 97.7°F (36.5°C)
- Heart rate: 160 beats/min
- Respiratory rate: High-frequency oscillatory ventilation
- Blood pressure: 61/37 mm Hg, mean 36 mm Hg
- Oxygen saturation: 99% (fraction of inspired oxygen 66% with oscillator settings of Hz=10 cycles/sec, amplitude=24, mean airway pressure=8.5 cm H<sub>2</sub>O)

#### Physical Examination (Postnatal Day 9)

- Weight: 740 g
- Head: Sutures widely separated; anterior fontanelle soft, open and flat; nondysmorphic facies; eyes fused
- Oral cavity: Endotracheal tube in place
- Lungs: Good chest wiggle down to pelvis
- Cardiovascular: Normal heart sounds, no murmur during brief pause of high-frequency oscillatory ventilation
- Abdomen: Soft, nondistended, few bowel sounds auscultated
- Genitourinary: Normal preterm male genitalia
- Neuro: Tone appropriate for gestational age
- Extremities: Warm and well-perfused, capillary refill 2 seconds, no edema
- Skin: Several gray-brown, thin, crusted plaques on mid-line of back with surrounding erythema

#### Laboratory Studies (Postnatal Day 9)

- White blood cell count: 13,400/ $\mu$ L ( $13.4 \times 10^9$ /L) with 53% neutrophils, 12% bands, 10% monocytes, and 15% lymphocytes

- Hemoglobin and hematocrit: 12.8 g/dL and 37%, respectively
- Platelet count:  $87 \times 10^3$ / $\mu$ L ( $87 \times 10^9$ /L)
- Blood urea nitrogen: 30 mg/dL (10.7 mmol/L)
- Creatinine: 0.94 mg/dL (83  $\mu$ mol/L)
- Glucose: 226 mg/dL (12.5 mmol/L)
- CRP: 30 mg/L (2.8 nmol/L)
- Blood culture, bacterial and fungal cultures from wound pending

#### Differential Diagnosis

- Blistering disorder, such as epidermolysis bullosa
- Burn
- Cutaneous aspergillosis
- Ecthyma gangrenosum
- Impetigo
- Noninfectious vasculitis
- Pyoderma gangrenosum

#### Actual Diagnosis

Primary invasive cutaneous aspergillosis of the neonate.

An increase in the size of lesions and exudate heightened the suspicion for infection. Because of the patient's extreme prematurity, the consulting dermatologist deferred a biopsy and instead performed a skin scraping on postnatal day 11, which demonstrated septate hyphae on potassium hydroxide preparation. Antifungal medication was changed from micafungin to liposomal amphotericin B. Wound culture was reported to be positive for *Aspergillus fumigatus*. Of note, there was ongoing construction in the NICU at the time of the infant's birth.

Given the infant's prematurity, surgical debridement was deferred. A hydrogel dressing was applied to the lesions with an overlying thin foam dressing and changed every other day for gentle debridement. Serum *Aspergillus* galactomannan test, which detects circulating *Aspergillus* cell wall elements, had a positive result, suggesting invasive disease. Evaluation for disseminated infection (abdominal and head ultrasonography, cerebrospinal fluid culture, and fungal blood culture) was negative. Ophthalmologic examination performed at 6 weeks of age was also negative for fungal infection.

Three days after treatment with liposomal amphotericin B, the serum creatinine increased and urine output decreased. Antifungal treatment was subsequently changed to intravenous voriconazole. Repeat *Aspergillus* galactomannan assays became negative 21 days after initiation of antifungal therapy with micafungin. The cutaneous lesions resolved after 28 days of total antifungal therapy (2 days micafungin, 3 days liposomal amphotericin B, 23 days voriconazole), and the infant continued to receive

voriconazole for 19 more days, for a total of 47 days of antifungal therapy.

## WHAT THE EXPERTS SAY

*Aspergillus* is a ubiquitous fungal organism, and *Aspergillus fumigatus* is the most common species that causes invasive disease in humans. Humans are infected via the respiratory tract by *Aspergillus* spores that are easily aerosolized because of their small size (2.5–3 µm diameter). Prior studies have demonstrated that *Aspergillus* outbreaks have occurred in hospitals undergoing construction, (1) and *Aspergillus* spores have been found on the walls of incubators of infected neonates. (2) The ability for *Aspergillus* organisms to cause invasive infection depends on the immunologic status of the host. Other risk factors for invasive disease include neutropenia and receipt of corticosteroids or antibiotics.

Cutaneous aspergillosis is a rare entity that occurs in high-risk groups, including premature neonates, burn victims, and immunocompromised patients. Cutaneous infection can occur through direct skin injury (primary cutaneous aspergillosis) or hematogenously (secondary cutaneous aspergillosis). Among neonates, prematurity is the most common risk factor, likely because of impaired immune response and impaired skin barrier function. (3) The humid environment of an incubator may cause skin maceration, and indwelling lines and use of tape and external leads can cause skin erosion, permitting invasion

of *Aspergillus* organisms (Fig 2). Initial lesions may appear as erythematous papules or plaques, but can transform to pustules, ulcerations, crusts, necrotic eschars, or purpura. (4) Rapid diagnosis and treatment of cutaneous aspergillosis are necessary to avoid dissemination of infection, which is associated with high morbidity and mortality. (5)

Cutaneous aspergillosis is diagnosed through tissue biopsy and culture. Histopathologic findings include septate hyphae with branching at 45 degrees, and invasion of dermal blood vessels may be visualized. Evaluation for dissemination of infection is imperative. The *Aspergillus* galactomannan test is a serum enzyme immunoassay that is a useful adjunct to diagnose early invasive infection and can be used to monitor response to therapy. (6)

Treatment of cutaneous aspergillosis typically involves both surgical debridement and systemic antifungal therapy, though there are reports of premature infants successfully treated with systemic antifungal therapy alone. (4) Amphotericin B, both in its conventional and liposomal formulations, is the most commonly used antifungal treatment for *Aspergillus* in the neonate. In older children and adults, voriconazole, a triazole antifungal, has emerged as the treatment of choice for invasive *Aspergillus* infections. In premature neonates, data regarding pharmacokinetics of voriconazole are limited, though case reports have documented its successful use. (7) We chose to use voriconazole because of impaired renal function in the index case. Therapeutic drug monitoring is recommended when

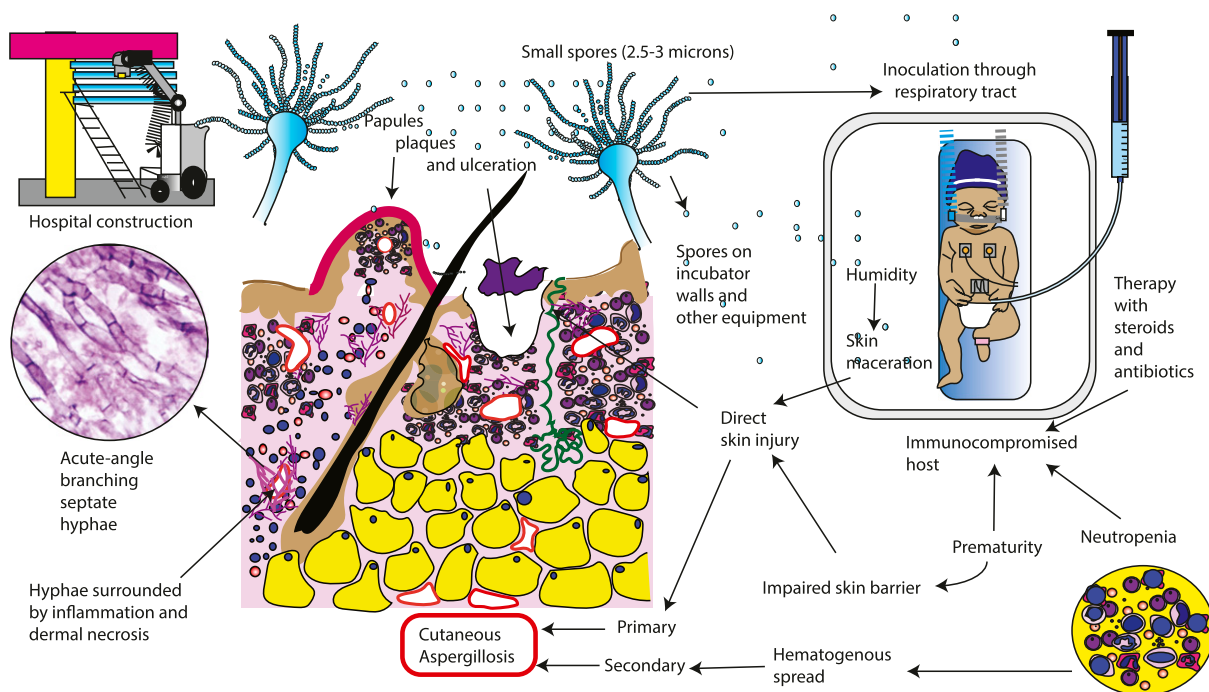


Figure 2. Pathogenesis of *Aspergillus* infection in the premature neonate. Drawn by Dr Lakshminrusimha.



voriconazole is administered to maximize effectiveness and minimize toxicity. When systemic antifungal therapy is given without surgical debridement, treatment course for cutaneous aspergillosis typically ranges from 3 to 8 weeks, depending on clinical response. When invasive disease is present, successful treatment has been reported with as little as 33 days of therapy. (4)(7)

Other etiologies that should be considered in the differential diagnosis of a neonate with necrotic plaques or eschars include infection such as ecthyma gangrenosum, which presents with a single or multiple ulcerating lesions with black eschar and surrounding erythema. It is typically caused by infection with *Pseudomonas aeruginosa*, though other organisms have been implicated in neonates, including *Escherichia coli*, and blood and wound cultures are typically positive for the causative organism. Though impetigo typically presents with vesicles, pustules, or bullae, superficial staphylococcal infections can present with crusted plaques without noticeable vesicles or pustules. These plaques are typically honey-colored, rather than gray-brown as noted in our patient. Culture of the lifted edge of a crusted plaque of impetigo would confirm the diagnosis.

Noninfectious etiologies considered in the differential diagnosis include noninfectious vasculitis, which typically presents with purpuric papules and/or plaques. Burns and thermal injury can also cause crusted plaques or eschars after initial bullae or erosion. In neonates, thermal injury has been described as a complication of the use of transillumination devices. Thermal injury was considered in our patient initially because the lesions were noted after the use of a bilirubin blanket directly to the back. With proper wound care, thermal injury should improve over time, not worsen as the cutaneous lesions did in this patient. Pyoderma gangrenosum is highly unusual in a neonate, but can present with sharply demarcated ulcers with characteristic undermined borders, often on the groin and buttocks in infants. Finally, an erosion or ulceration with overlying crust may be secondary to a primary blistering disorder, such as epidermolysis bullosa. This was not considered in this patient because of the lack of friction-induced erosions, mucosal erosions, and/or nail abnormalities.

## SUMMARY

- Primary cutaneous aspergillosis should be considered in the differential diagnosis of a cutaneous lesion of an

extremely low-birthweight infant, especially if there is ulceration or necrosis.

- Skin biopsy is the preferred means to diagnose cutaneous aspergillosis.
- Treatment with systemic antifungal therapy may be curative in extremely low-birthweight infants, many of whom are not good candidates for surgery. Voriconazole is a triazole antifungal compound with fungicidal activity against *Aspergillus* and has been successfully used in preterm infants.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of neonatal fungal infections.
- Know the clinical manifestations and diagnostic features of neonatal fungal infections.
- Know the treatment and complications of neonatal fungal infections.

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## Visual Diagnosis: An Extremely Preterm Neonate with Gray Plaques on the Back

Natasha A. Nakra, Smita Awasthi, Satyan Lakshminrusimha and Vaneet Kalra

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## Pregnancy Complicated by Type 2 Diabetes Mellitus

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

**AUTHOR DISCLOSURE** Dr Demasio has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and

American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## PRESENTATION

### History

A woman was sent from her prenatal office visit to the labor and delivery (L&D) department for triage evaluation because of new-onset hypertension and nondependent edema. She was 35 years old and a primigravida who was at 37 6/7 weeks of gestation. The FHR tracing on arrival, as shown in Fig 1, was nonreactive.

The antenatal course was complicated by type 2 diabetes mellitus diagnosed approximately 5 years before this pregnancy, and she took oral hypoglycemic medication for 3 years before conception. Insulin was recommended at the start of the pregnancy, but she delayed starting the medication, opting for a second opinion. After changing her prenatal care site, she was prescribed subcutaneous insulin by the maternal fetal medicine subspecialist, and at the time of this hospital admission, she was taking a total daily

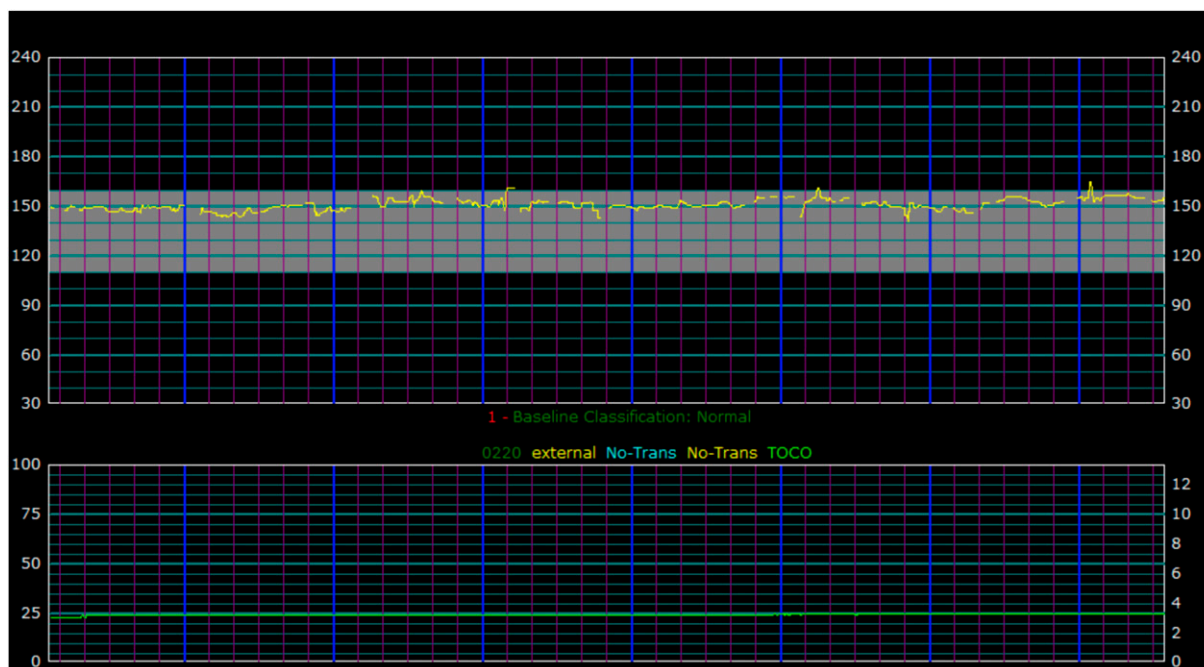


Figure 1. Electronic fetal monitoring strip 1.



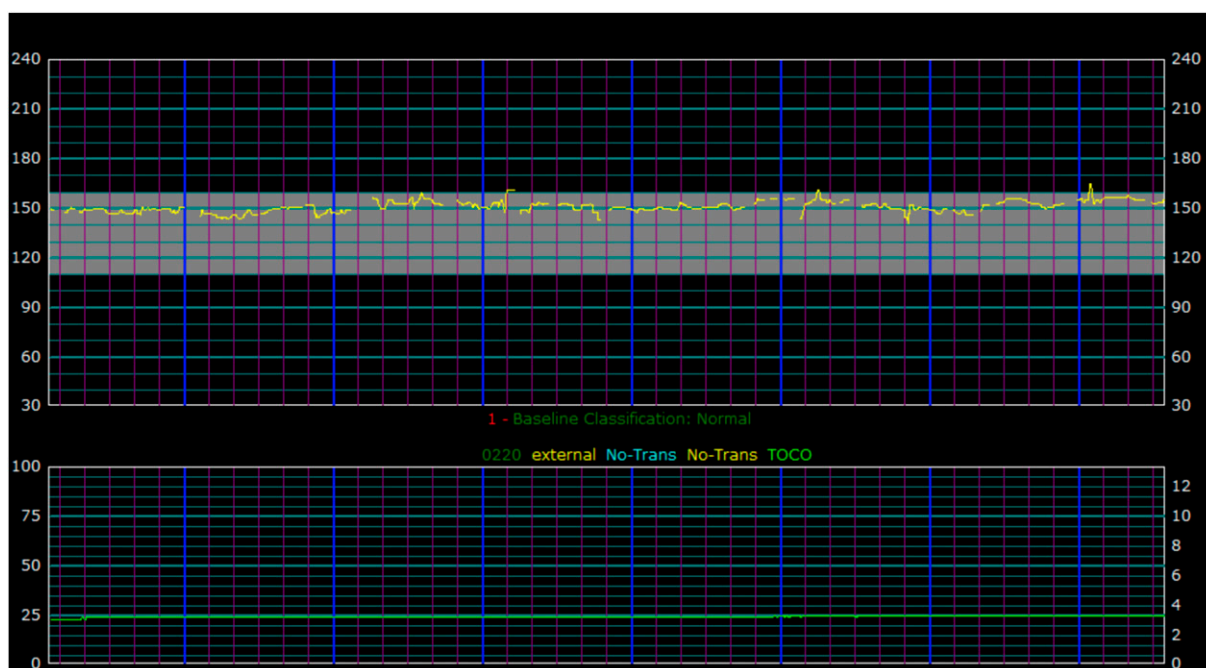


Figure 1. Electronic fetal monitoring strip 1.

dose of 121 units of combined long- and short-acting insulin in divided doses. This is in comparison to a calculated weight-based dose of 30 to 35 units daily. She rarely provided home glucose values, and when she did, fasting glucose values were significantly elevated above 95 mg/dL (5.2 mmol/L) and ranged from 107 to 193 mg/dL (5.9–10.7 mmol/L). She was hospitalized once during the

antepartum course for glucose control. Her hemoglobin A<sub>1c</sub> was 6.2% at the start of the pregnancy and increased to 6.9% by the third trimester. She also had a history of abdominoplasty that was performed 1 year before the pregnancy. The baseline timed urine collection at 16 weeks of gestation revealed proteinuria of 242 mg per 24 hours. In the third trimester, she received fetal monitoring with

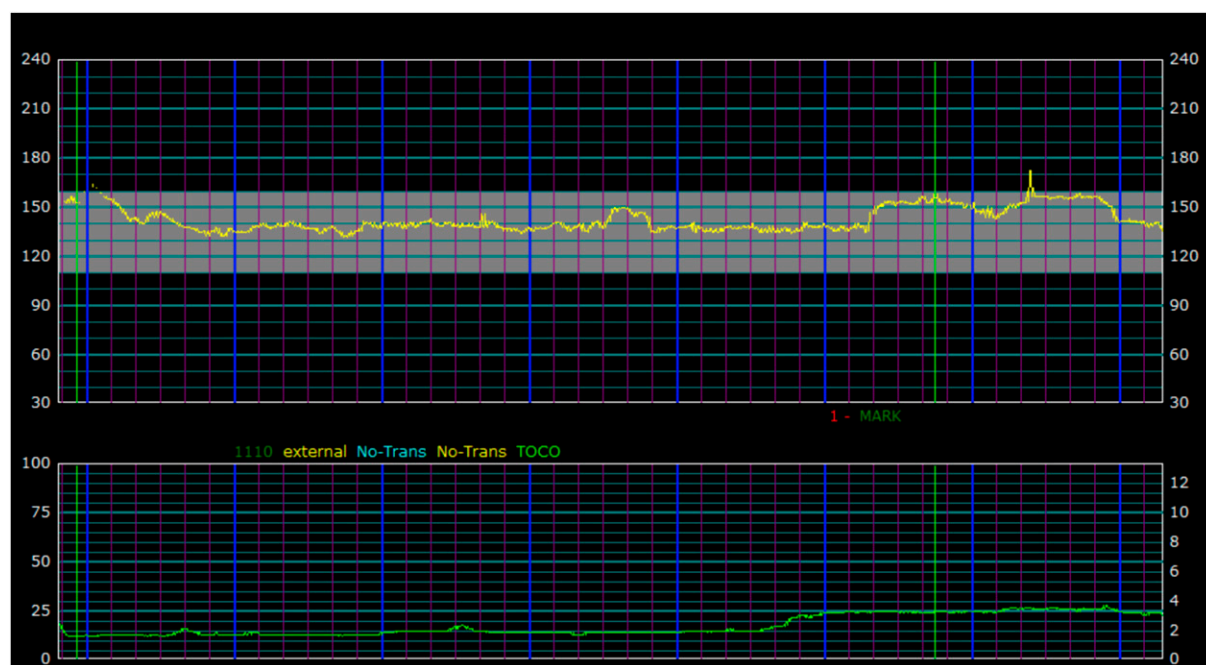


Figure 2. Electronic fetal monitoring strip 2.

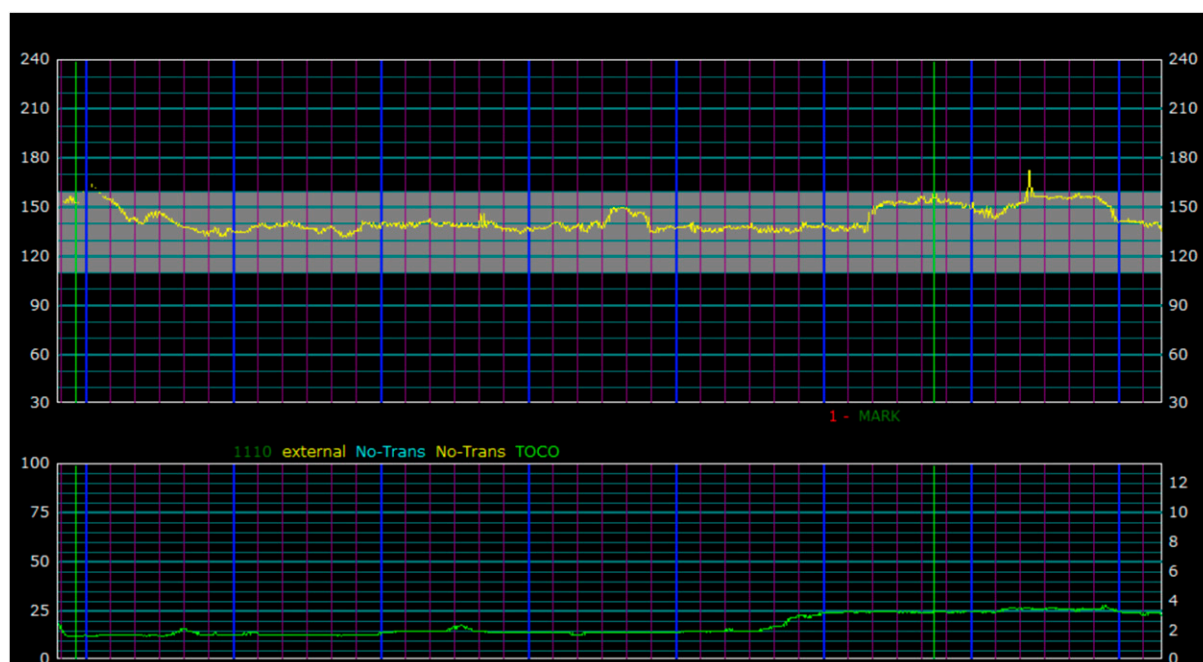


Figure 2. Electronic fetal monitoring strip 2.

weekly nonstress tests, and the last FHR tracing before admission to L&D was reactive (Fig 2).

On admission to the L&D department, her blood pressure was 140/93 mm Hg and her pulse was 104 beats/min, she was afebrile, and had a body mass index of 51 kg/m<sup>2</sup>. The point-of-care glucose concentration was elevated at 174 mg/dL (9.6 mmol/L), leading to treatment with

subcutaneous insulin. Her cervix was 1 cm dilated, not effaced, and the presenting part was at a high station. The estimated fetal weight based on ultrasound examination performed that week was 2,871 g. Labor induction was started with prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) vaginal insert because of a concern about the nonreactive FHR tracing (Fig 3).

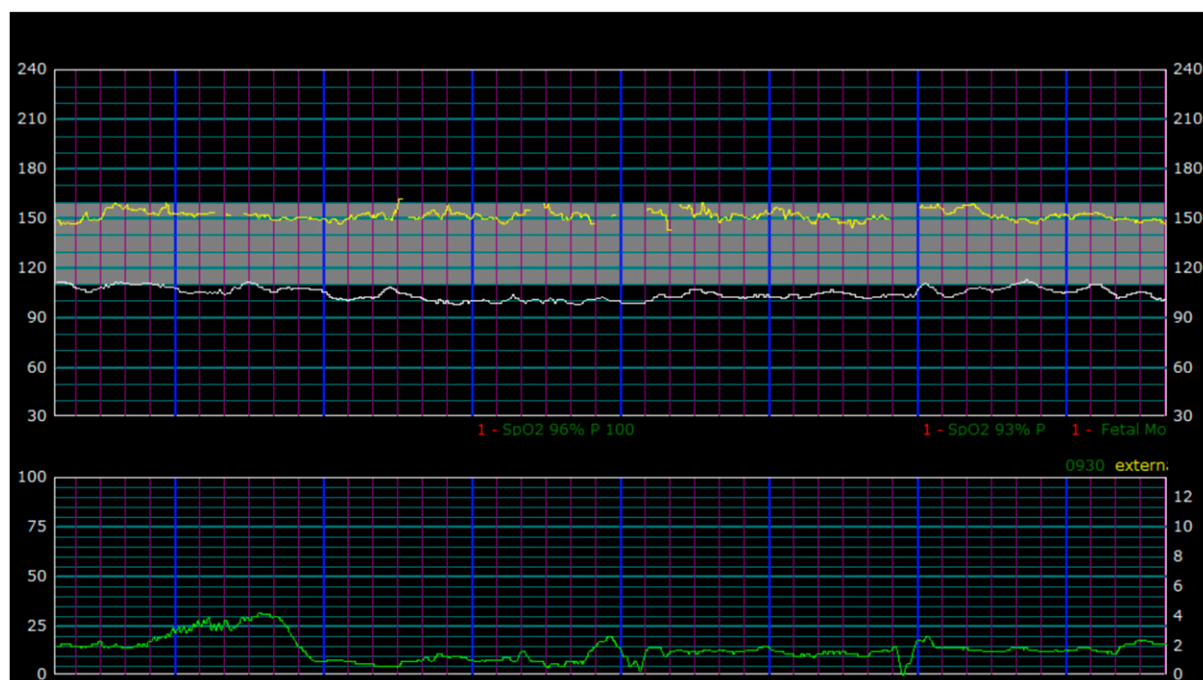


Figure 3. Electronic fetal monitoring strip 3.

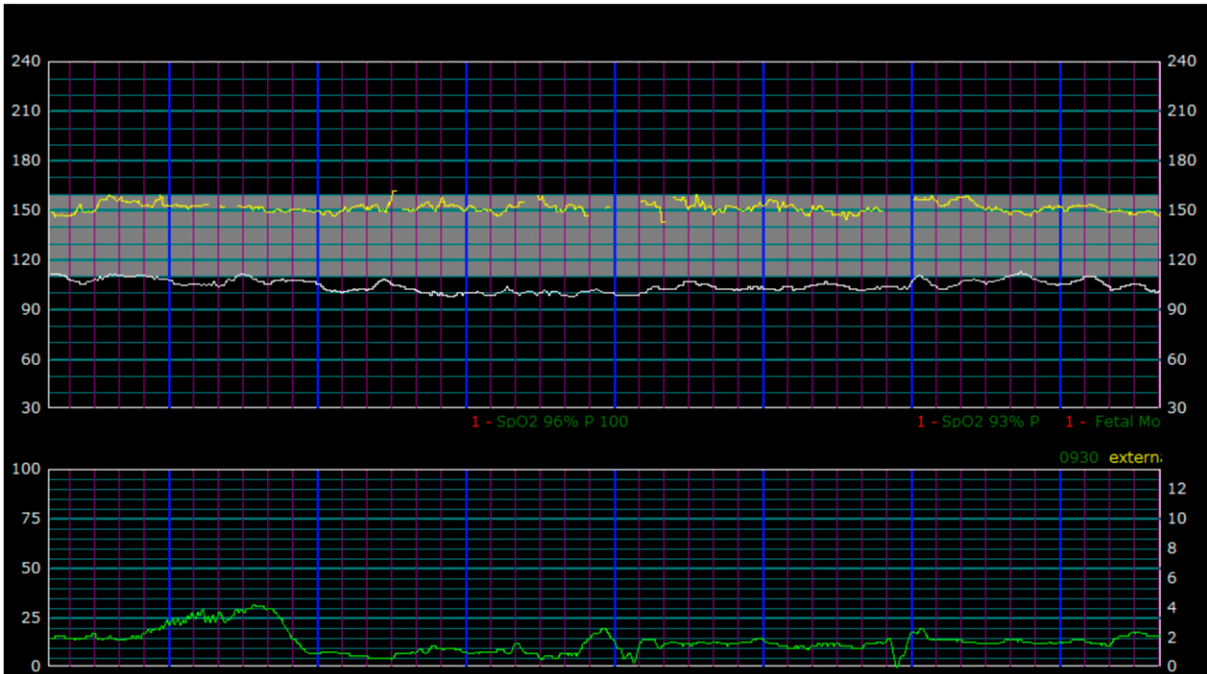


Figure 3. Electronic fetal monitoring strip 3.

After 9 hours, the PGE<sub>2</sub> insert was unintentionally expelled. The cervix, although more effaced at 80%, was still only 1 cm dilated and at -3 station. The FHR tracing was category 1 (Fig 4) and therefore, the induction was continued with intracervical Foley catheter and intravenous oxytocin

augmentation. She requested epidural analgesia, which was administered.

Twenty-four hours after the start of labor induction, her systolic blood pressure was persistently elevated above 160 mm Hg, leading to the start of intravenous magnesium

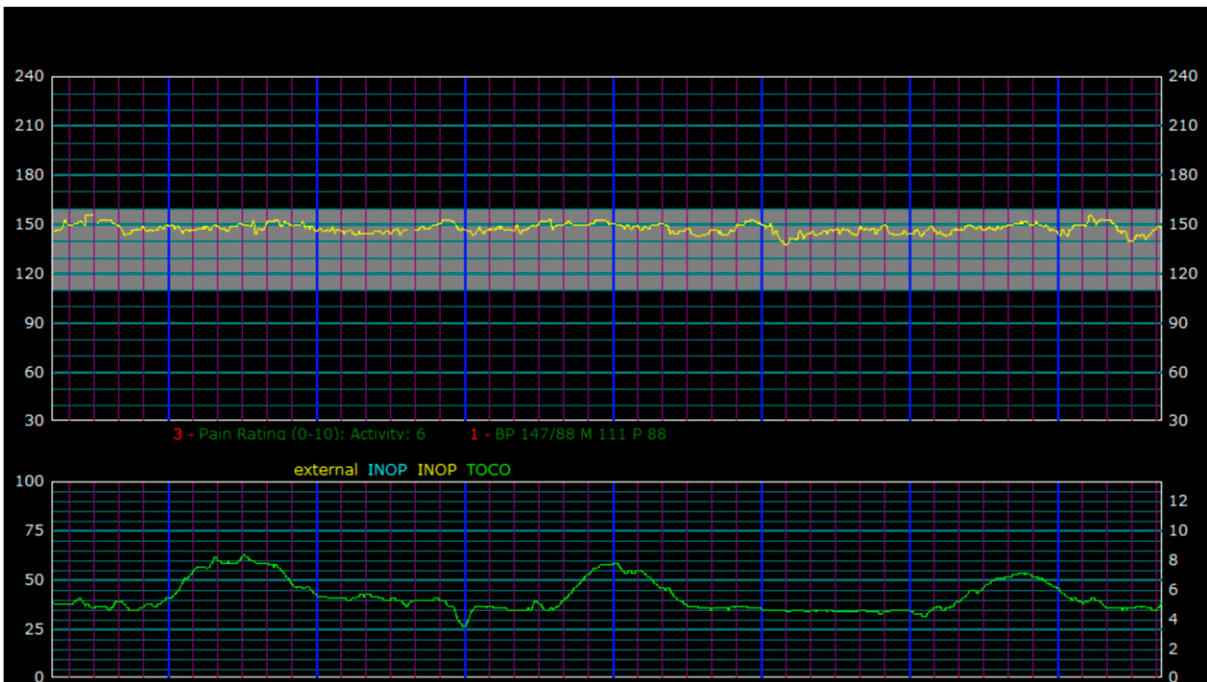


Figure 4. Electronic fetal monitoring strip 4.

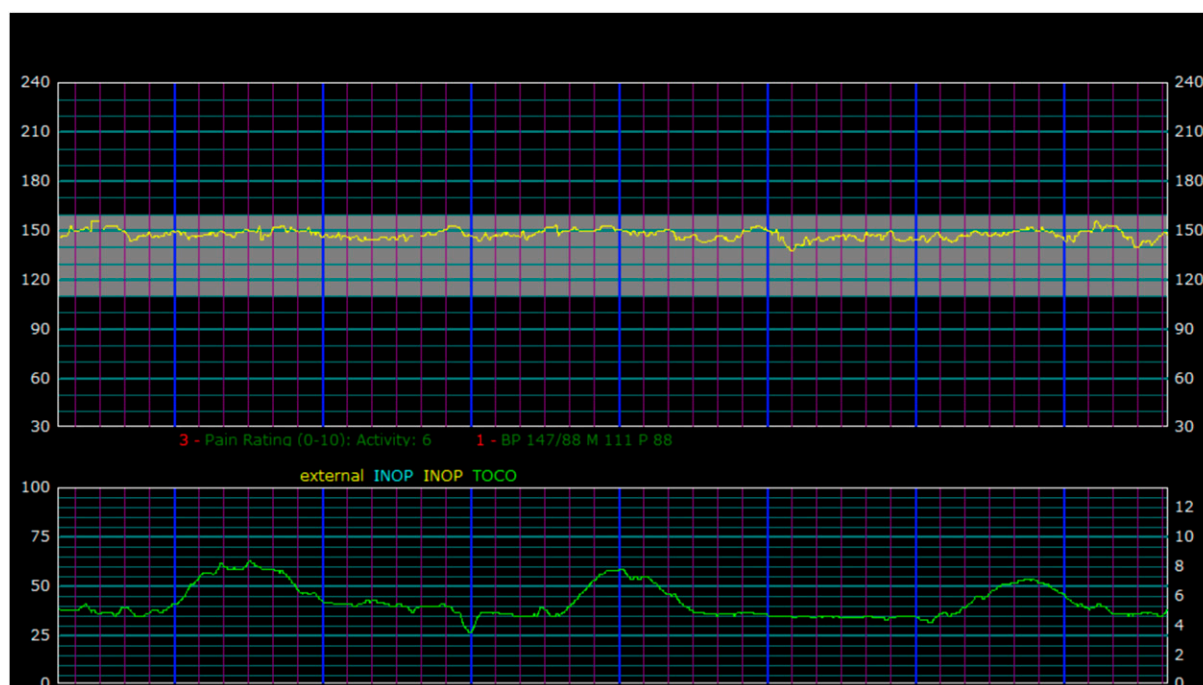


Figure 4. Electronic fetal monitoring strip 4.

sulfate for seizure prophylaxis. She required intravenous labetalol to control the elevated blood pressure, and a diagnosis of severe preeclampsia was made. The cervix was 4 cm dilated, 80% effaced, and the station was unchanged at -3 after the intracervical Foley catheter was expelled. She underwent artificial rupture of membranes

2 hours later and clear amniotic fluid was noted. At this time, an intrauterine pressure catheter was inserted for better assessment of contraction strength and titration of oxytocin. After these interventions were performed, the FHR tracing shown in Fig 5 was noted. Also noted was repeated maternal desaturation to 90% (Fig 5, pulse

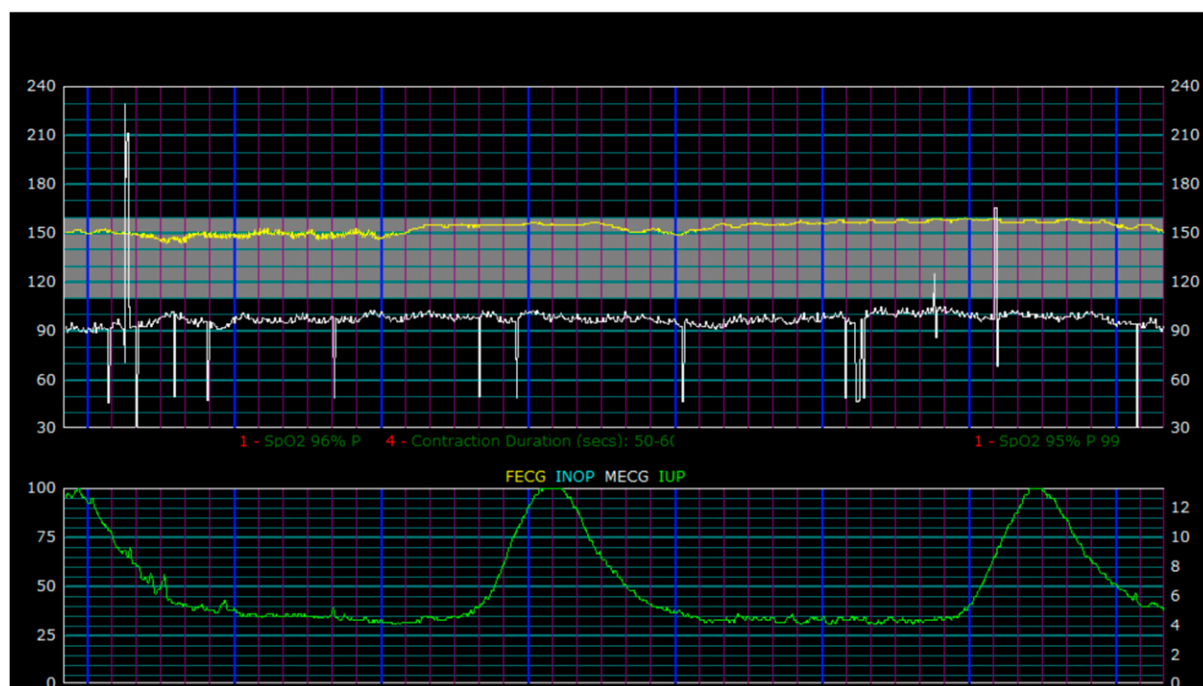


Figure 5. Electronic fetal monitoring strip 5.



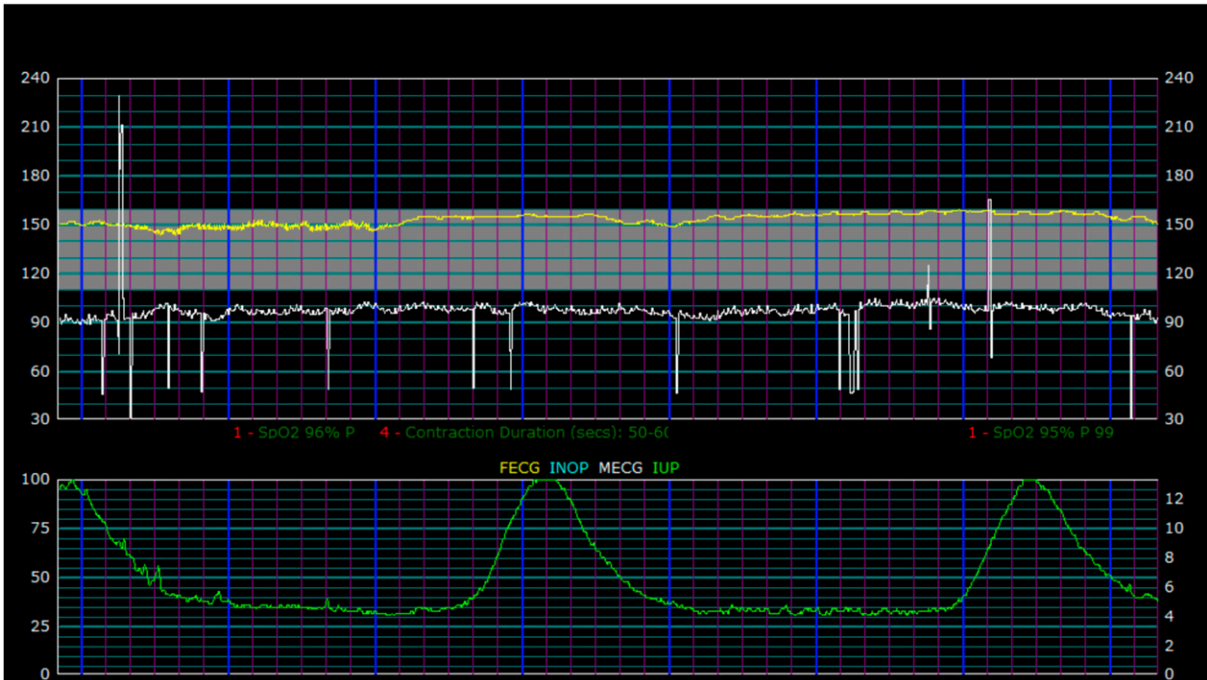


Figure 5. Electronic fetal monitoring strip 5.

oximetry tracing, white line) treated with the administration of oxygen. The desaturations led to the revelation of a historical diagnosis of obstructive sleep apnea. Eight hours passed, for a total of 34 hours from the start of the induction, and her cervix was still 4 cm dilated with the station at -3.

The FHR tracing, shown in Fig 6, was considered reassuring even though the baseline had increased. Her blood glucose concentration had been maintained at less than 120 mg/dL (6.6 mmol/L) for the duration of the labor course after the high admission value. A diagnosis of failed induction of labor was made and a primary cesarean

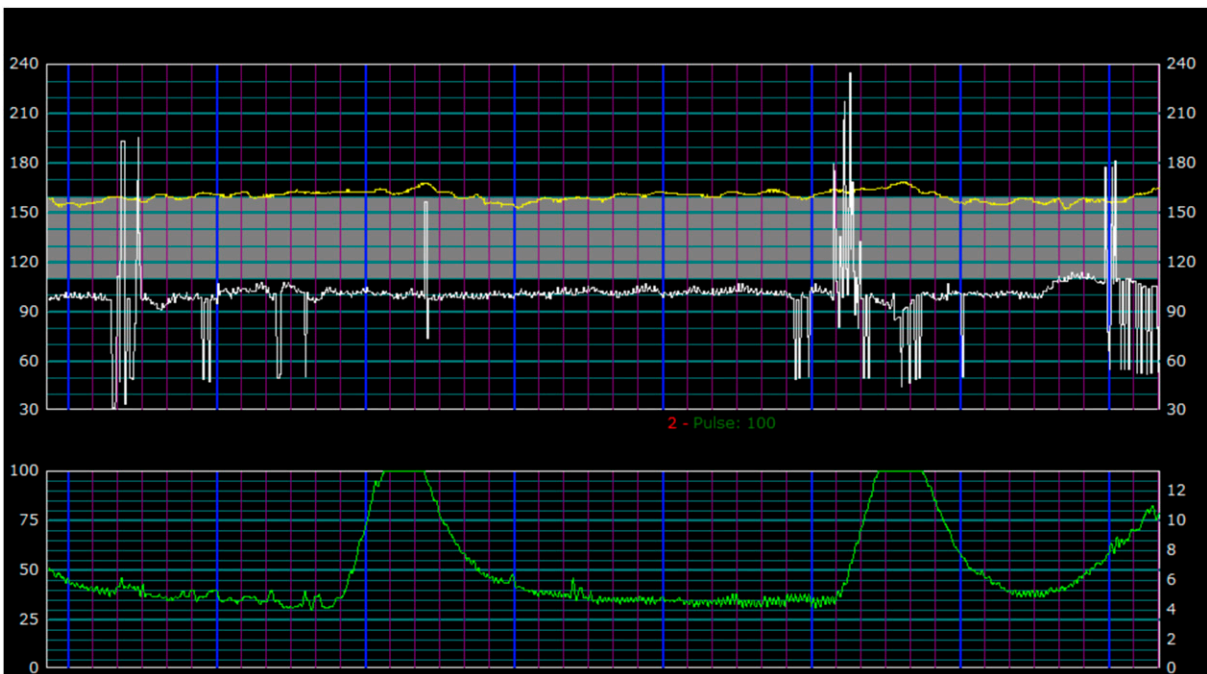


Figure 6. Electronic fetal monitoring strip 6.

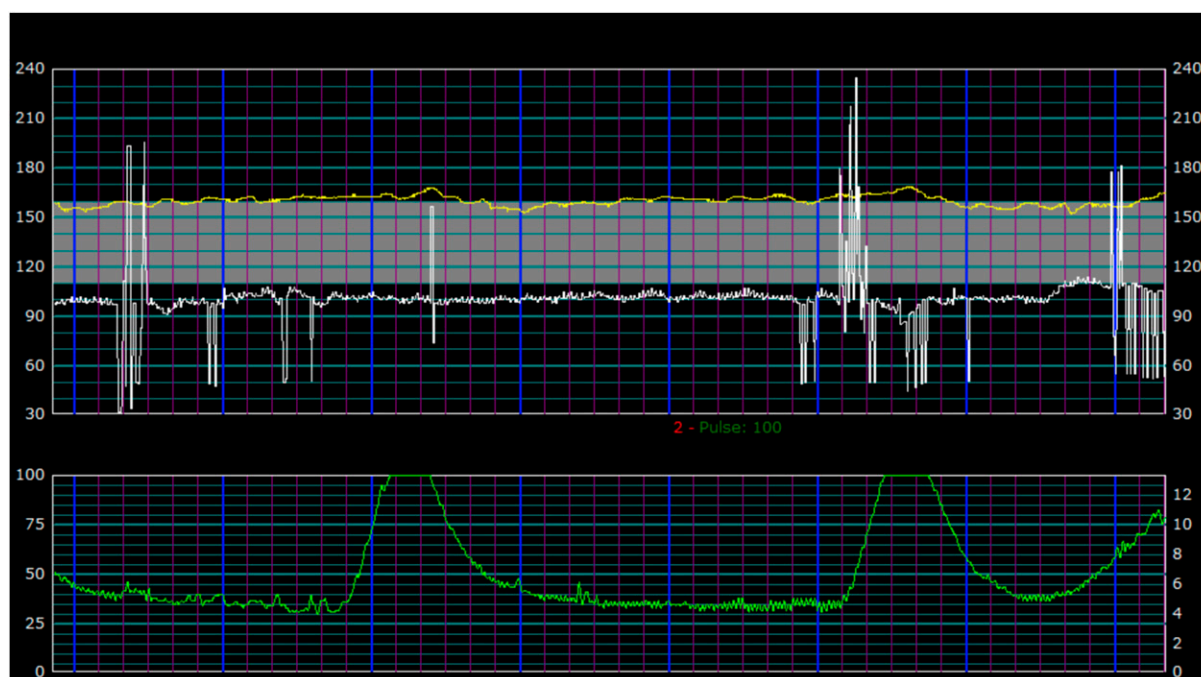


Figure 6. Electronic fetal monitoring strip 6.

delivery was performed. A viable male infant was delivered with a birthweight of 3,270 g. The Apgar score was 7 at 1 minute, and 9 at 5 minutes after birth. The umbilical cord blood gases are shown in Table 2.

TABLE 2. Umbilical Cord Gas Values for the Patient

CORD GASES	PATIENT RESULT	REFERENCE RANGE
<b>Arterial</b>		
pH	7.19	7.35–7.45
Pco <sub>2</sub> , mm Hg	79	35–45
O <sub>2</sub>	14	18–100
Base excess, mEq/L (mmol/L)	1.6	10 to 2
HCO <sub>3</sub> , mEq/L (mmol/L)	29	22–28
<b>Venous</b>		
pH	7.27	7.35–7.45
Pco <sub>2</sub> , mm Hg	59	35–45
PO <sub>2</sub> , mm Hg	23	80–100
Base excess, mEq/L	–0.10	10 to 2
HCO <sub>3</sub> , mEq/L (mmol/L)	26	22–28

## DISCUSSION

The intrapartum management for women who have pregestational diabetes can be particularly challenging. Pregnancies complicated by type 1 or type 2 diabetes have an increased risk for adverse perinatal outcomes such as hypertensive diseases of pregnancy, preterm labor, and cesarean delivery. In addition, the perinatal mortality for infants of diabetic mothers is 3 times greater than for infants of nondiabetic mothers. (1) Although major fetal anomalies significantly influence perinatal mortality in this population, 1 study demonstrated that when anomalous fetuses are excluded in women with preexisting diabetes, stillbirth at more than 20 weeks of gestation was 4 times greater than in those without diabetes. (2) The risk of stillbirth was 29.7 per 1,000 deliveries, and although the majority of the fetal deaths were antepartum, 3 (6.5%) of 46 deaths occurred intrapartum. (2) The high risk of stillbirth is the basis for intensive maternal and fetal surveillance using nonstress testing and ultrasonography to monitor the fetal status before the onset of labor, and earlier delivery for women with pregestational diabetes, or gestational diabetes requiring insulin.

It is well-established that maternal hyperglycemia, such as occurs with ketoacidosis will produce abnormal FHR tracings, and correction of the metabolic derangement will resolve the tracing abnormalities. However, few studies examine the intrapartum FHR tracings of diabetic and



nondiabetic women to determine how they correlate with the development of fetal acidosis. One retrospective case-control study compared short-term outcomes of diabetic and nondiabetic women in labor who had nonreassuring FHR tracings requiring scalp blood sampling (scalp pH). The authors found that the arterial umbilical cord pH of the diabetic neonates was significantly decreased compared with the nondiabetic controls. The venous pH and 5-minute Apgar scores were similar between the 2 groups. (3) The authors suggest that fetuses of women with pre-existing diabetes or women with insulin-dependent gestational diabetes mellitus have a lower arterial pH and may be more prone to acidosis. Further studies are required to determine whether certain intrapartum FHR patterns that are associated with acidosis are more ominous for women with diabetes, and whether pregnancy outcomes with these tracing abnormalities are different for diabetic and nondiabetic neonates.

Although an intrapartum euglycemic state was maintained for the woman in this case, she had poor antepartum glucose control and developed preeclampsia. She had several other risk factors for poor placental development and fetal oxygenation such as sleep apnea, obesity, a long labor induction, and cesarean delivery. However, similar to the Reif et al study, the venous pH, reflecting maternal and placental gases, and the 5-minute Apgar score, were normal. (3) The arterial pH, however, reflecting fetal oxygenation did show mild acidosis (pH <7.20, Table 2) in the

absence of any abnormal FHR patterns, such as recurrent decelerations or prolonged decelerations, suggesting that this fetus was prone to developing acidosis.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor, including reassuring and nonreassuring and indeterminate patterns.

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## Strip of the Month: Pregnancy Complicated by Type 2 Diabetes Mellitus

Kafui A. Demasio

*NeoReviews* 2019;20:e306

DOI: 10.1542/neo.20-5-e306

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# Neonatal Hemophagocytic Lymphohistiocytosis

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## Education Gaps

1. Hemophagocytic lymphohistiocytosis is rarely seen in the neonatal population.
2. Clinicians should be able to identify and evaluate neonates with disorders of immune regulation.

## Abstract

Hemophagocytic lymphohistiocytosis (HLH) is extremely rare in the neonatal period. The incidence of neonatal HLH is not confirmed and may range from 1 in 50,000 to 150,000. The incidence varies based on ethnicity, particularly in populations in which consanguinity is common. HLH is associated with a high fatality rate and poor prognosis, making it important to recognize and diagnose it early. This review will concentrate primarily on the diagnosis and management of neonatal HLH.

## Objectives After completing this article, readers should be able to:

1. Review the pathophysiology and clinical features of hemophagocytic lymphohistiocytosis (HLH).
2. Describe the criteria for diagnosis of HLH in the neonatal population.
3. Review the management recommendations for neonates with HLH.

## INTRODUCTION/EPIDEMIOLOGY

Hemophagocytic lymphohistiocytosis (HLH) belongs to a group of disorders known as histiocytosis, which is characterized by an overabundance of tissue macrophages or histiocytes. Histiocytes are phagocytic cells present in connective tissue, which normally participate in the innate immune system by triggering cell signaling and activation. (1)(2) In effect, HLH can concisely be defined as a hyperinflammatory syndrome of pathologic immune activation. (3) The term HLH originated from its distinct histomorphologic findings described as an accumulation of lymphocytes and histiocytes containing phagocytosed cells in various tissues (Fig 1). (3)(4)(5)(6) This syndrome could be either familial or sporadic, which can be difficult to differentiate at the time of initial presentation. (3)(5)

**AUTHOR DISCLOSURE** Drs McLean, Katebian, Suh, Mirza, and Amin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

FDA	Food and Drug Administration
fHLH	familial hemophagocytic lymphohistiocytosis
HLH	hemophagocytic lymphohistiocytosis
IFN $\gamma$	interferon $\gamma$
NK	natural killer
sCD25/sIL-2R	concentration of soluble interleukin 2 receptor
SCT	stem cell transplantation

Clinical presentation of HLH in the neonatal period is extremely rare. (7) The incidence of neonatal HLH is not confirmed and may range from 1 in 50,000 to 150,000. Tertiary care pediatric centers should expect 1 case per 3,000 inpatient admissions. (2)(8) The incidence varies based on ethnicity, particularly in populations in which consanguinity is common. (2)(9) In North America, blacks may represent up to 1 in 5 cases of familial HLH. (10)

HLH is associated with a high fatality rate and poor prognosis, pointing to the importance of early recognition and diagnosis. This review will concentrate primarily on the diagnosis and management of neonatal HLH.

## **PATHOPHYSIOLOGY**

The terms “familial” (fHLH) or “primary HLH” are often used to indicate cases of HLH caused by an underlying genetic disorder. The genetic mutation can be autosomal recessive or X-linked, based on whether the gene mutation occurred within the fHLH loci or in a gene responsible for an immune deficiency. Of all cases of fHLH, 70% to 80% present before 1 year of age. (11) Of those with fHLH presenting before 1 year of age, 90% are asymptomatic in the first month after birth. (1)(3)(8)(11) It is estimated that 20% to 40% of FHLH cases result from mutations at the fHLH2 loci within the perforin gene (*PRF1*) on chromosome 10q22.1. (5)(7) More than 40 perforin gene mutations have been identified, many of which are reported as recurring in consanguineous families of Turkish, African, African American, and Japanese descent. (4)(9)(10)

Perforin is secreted by both cytotoxic T lymphocytes and natural killer (NK) cells. Perforin enables these cells to perforate cell membranes, allowing granzyme B to enter and initiate cell death via an apoptotic pathway. (Fig 2) When perforin is absent, cytotoxic T cell and NK cell signaling remains activated, resulting in the continual production of inflammatory cytokines and activated macrophages. Subsequent accumulation of lymphohistiocytic infiltrates in

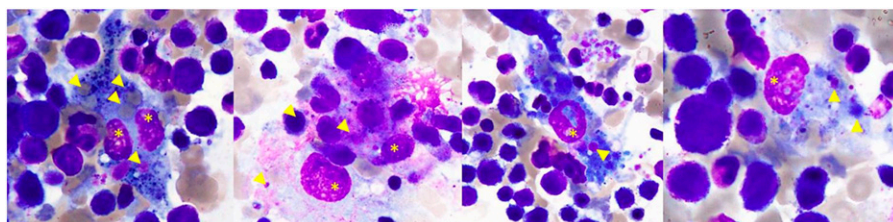
almost all organ systems leads to the clinical signs and symptoms of HLH frequently seen at diagnosis. (4)(9)

Studies have also identified mutations in genes as causes of fHLH, including FHL3: *UNC13D* (codes for Munc13-4), FHL4: *STX11* (Syntaxin 11), and FHL5: *STXBP2* (Munc18-2). These genes play critical roles in the initial steps of cytolytic granule secretions and in their absence, cytolytic granule exocytosis and activity remain ineffective. (1)(5)

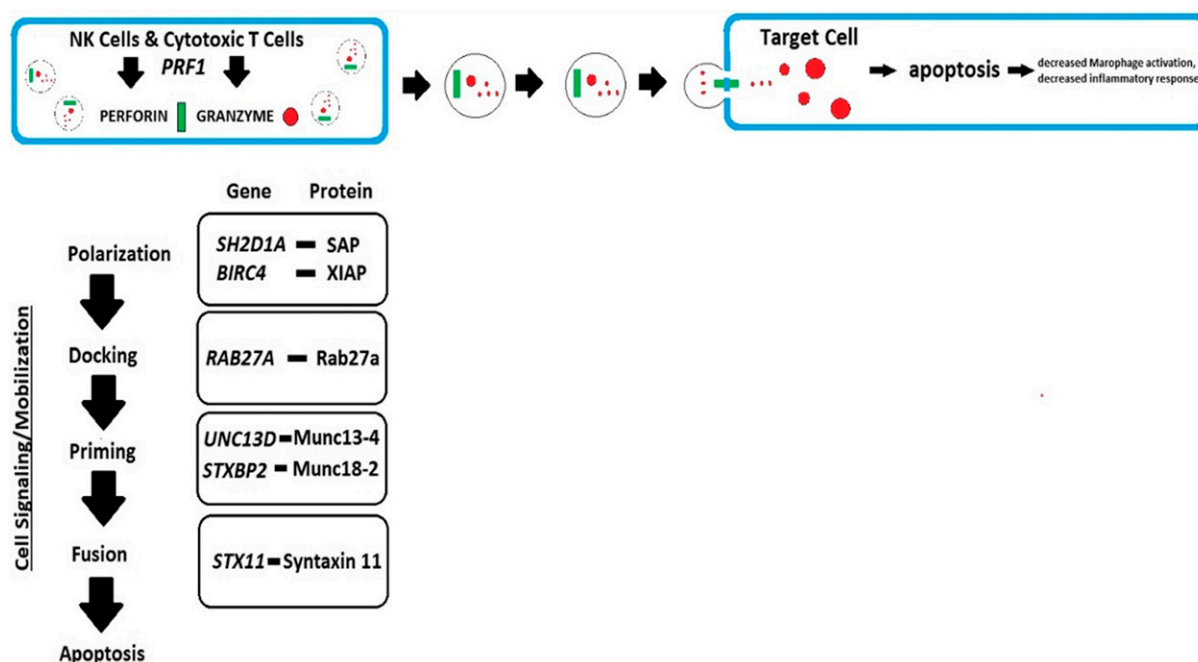
In North America, 7 genes are found to be commonly associated with HLH: *PRF1*, *UNC13D*, *RAB27A*, *STX11*, *SH2D1A*, *BIRC4*, or *STXBP2*. (1)(8)(12) As stated before, *PRF1* codes for perforin/granzyme B proteins. *SH2D1A* codes for Sap protein expression and *BIRC4* codes for XIAP protein expression; both of these are required for polarization of cytolytic granules. All others code for CD107a mobilization (Fig 2). Deficiencies in these genes lead to abnormal cytotoxic function by NK and T cells. (8)(13) Of note, the *LYST* gene is also considered diagnostic but is not commercially available, though it is available for testing by next-generation sequencing at Cincinnati Children’s Hospital in Cincinnati, OH. Suspected boys should be tested for all 7 genes whereas girls do not need to be tested for *SH2D1A* and *BIRC4* because they do not carry these genes. (8)

Of the numerous genes associated with HLH, few gene mutations have been linked to HLH in children younger than 1 month. (8) According to a review of neonates with HLH, the only genes found to be associated were *PRF1* and *UNC13D*. Of the 2, *PRF1* was found to be the predominant gene and more likely to be found in black and Hispanic patients, whereas mutations in *UNC13D* were more common in white patients. (8) These findings are similar to those from other studies reporting *PRF1* in older black patients with HLH. (10)

Genetic mutations associated with immune deficiency syndromes have also been implicated in fHLH. Mutations in *RAB27A* are associated with Griscelli syndrome, *SH2D1A* and *BIRC4* with X-linked lymphoproliferative disease, and *LYST* with Chediak-Higashi syndrome. Continued gene



**Figure 1.** Representative bone marrow aspirate images from a suspected case of hemophagocytic lymphohistiocytosis demonstrating numerous histiocytes (asterisk indicates histiocyte nuclei) that show engulfed debris. Areas of specific erythrocyte debris (yellow arrowheads) confirm hemophagocytic activity. (Wright-Geimsa stain, original magnification  $\times 1,000$ )



**Figure 2.** Perforin is secreted by both cytotoxic T lymphocytes and natural killer (NK) cells. Perforin plays a critical role in enabling proapoptotic granzymes to perforate cell membranes and initiate cell death via an apoptotic pathway. When perforin is absent, cytotoxic T cell and NK cell signaling remains activated, resulting in the continual production of inflammatory cytokines and activated macrophages. Hemophagocytic lymphohistiocytosis (HLH)-associated gene mutations may disrupt the normal cell signaling and mobilization process at the level of polarization, docking, priming, or fusion. Mutations in this pathway lead to similar HLH phenotypes with varying degrees of severity.

discovery related to fHLH will expand our understanding of its pathophysiology and lead to earlier diagnosis of neonatal HLH.

The term “secondary HLH” is used to indicate HLH acquired after a strong immunologic activation resulting from severe infection, rheumatoid disorders, malignancies, metabolic disorders, or prolonged intravenous nutrition (fat overload syndrome). (5) Infections known to cause excessive immune stimulation include Epstein-Barr virus, parvovirus B19, and cytomegalovirus. Bacteria, parasites, and fungi may have similar effects as well. (14) Neonatal cases are almost exclusively primary, and an analysis of these infectious etiologies is out of the scope of this review.

## DIAGNOSIS

To establish the diagnosis of HLH, a molecular diagnosis must be made consistent with HLH or the presence of at least 5 of the 8 diagnostic criteria. Diagnostic criteria were first published by the Histiocyte Society in 1994. (15) After the first identifiable gene linked to HLH was found in 1999 (16) and additional causative genes were subsequently identified, the committee revised its recommendations in 2004. The committee endorsed the suggestion that any molecular finding of primary HLH would no longer require further clinical or laboratory criteria for diagnosis.

The 8 criteria for diagnosis are persistent fever, splenomegaly, cytopenias, hypofibrinogenemia and/or hypertriglyceridemia, hyperferritinemia, hemophagocytosis, low NK cell activity, and high concentration of soluble interleukin 2 receptor (sCD25/sIL-2R) (Table 1). Low NK cell activity is the result of disruption of NK activity. Hemophagocytosis results from the deposition of lymphocytes/histocytes in tissues. Cytopenias are caused by high levels of specific inflammatory markers suppressing hematopoiesis and increasing overall apoptosis. Splenic macrophage proliferation and activation lead to splenomegaly. Secretion of plasminogen activator causes lysis of fibrinogen, leading to an overall decrease in fibrinogen levels. (17)(18) Hyperferritinemia is thought to be secondary to increased levels of the enzyme heme-oxygenase released from macrophages, which releases ferritin as a by-product during heme degradation. (17)(19) Other inflammatory markers found in excess inhibit lipoprotein lipase, leading to increased triglycerides. (17)(18) sCD25 can reflect activated T-cell activity because it is a transmembrane protein that is upregulated with T-cell activation. (19) Hyperthermia found in patients with HLH is from an overabundance of inflammatory mediators. (20)

Data on the best clinical diagnostic approach are conflicting. (8)(21)(22) Some consider sCD25/sIL-2R as the most useful biomarker, because it indicates inflammatory

**TABLE 1. 2004 Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis (5)**

Must fulfill either 1 or 2:

1. Molecular diagnosis: perforin, hMUNC 13-4, other relevant genes, flow cytometry for perforin in NK cells and cytotoxic T cells
2. 5 of 8 of the following criteria
  - a. Persistent fever\*
  - b. Splenomegaly\*
  - c. Cytopenias\*<sup>†</sup>
  - d. Hypofibrinogenemia (<150 mg/dL [ $<4.4 \mu\text{mol/L}$ ]) and/or hypertriglyceridemia (>265 mg/dL [ $>3.0 \text{ mmol/L}$ ])\*
  - e. Hyperferritinemia (>500 ng/mL [ $>1,123 \text{ pmol/Lng/mL}$ ])
  - f. Hemophagocytosis\*
  - g. Low natural killer cell activity
  - h. High concentration of soluble interleukin 2 receptor (sCD25/sIL-2R)

\*1994 criteria.

<sup>†</sup>Hemoglobin concentration less than 9 g/dL (90 g/L), neutrophils less than  $1.0 \times 10^3/\mu\text{L}$  ( $1.0 \times 10^9/\text{L}$ ), or platelets less than  $100 \times 10^3/\mu\text{L}$  ( $100 \times 10^9/\text{L}$ ) are considered diagnostic.

activity and disease process more accurately than ferritin and fibrinogen. (8)(20)(22)(23) However, ferritin levels greater than 10,000 g/dL ( $>22,470 \text{ pmol/Lng/mL}$ ) have been shown to be highly sensitive and specific for HLH diagnosis. (24) Others report that triglycerides are more useful and cost-effective indicators of HLH, but case studies have shown that triglycerides are elevated less often in neonatal HLH (likely because of rates of lipid metabolism). (21)(25)

The pathologic evaluation for hemophagocytosis is difficult because of the lack of consistent guidelines and absence of established criteria for quantifying hemophagocytic histiocytes in marrow aspirates. (26) Compounding this difficulty is the lack of specificity of finding hemophagocytic histiocytes because many common NICU events, such as blood transfusions, recovery from major surgical procedures, and sepsis, can all show a significant increase in hemophagocytic histiocytes. (26)(27)(28)(29) According to published literature, the presence of hemophagocytosis has a sensitivity of 83% and a specificity of only 60% in diagnosing HLH. (30)

This nonspecific occurrence of hemophagocytic histiocytes in the marrow (even when numerous) underscores the importance of caution that an isolated finding of hemophagocytosis lacks specificity and does not necessarily implicate a diagnosis of HLH immediately. Despite this, bone marrow

biopsy examination remains valuable in cases in which clinical suspicion for HLH is high. In such cases, bone marrow evaluation helps to exclude other processes involving the marrow, or other primary marrow disease.

Changes have been proposed to the current diagnostic principles because many of the criteria do not depict common features of the disease process. (8) Liver enzymes are currently not taken into account even though almost all cases have some level of liver inflammation. (7)(9)(31) Others have also raised concerns that neurologic criteria have not been considered even though neurologic abnormalities are a common clinical finding in children with HLH. (8)(23)(32) Similarly, there is no consideration for a family history for HLH even though there are proven genetic components of the disorder. (1)(12)(33)(34)(35)

## CLINICAL MANIFESTATIONS

If genetic testing is unavailable, inconclusive, or pending, the diagnosis of HLH can be made based only on clinical and laboratory criteria. The signs and symptoms of HLH vary in all ages and often are mistaken for other common disorders. In a review of 113 patients younger than 15 years for the anticipated 2004 updates, the Histiocyte Society found that the most common clinical signs in all cases were fever, hepatosplenomegaly, and cytopenias. (5) Numerous published reports have found hydrops and elevated transaminases to be the most common findings in the neonatal population. (5)(9)(31)(36)(37)

In contrast with the findings of the HLH Society, hypothermia is more common than hyperthermia in neonates with HLH (4)(31)(32)(38); however, data are limited on hypothermia duration and severity. Nonenvironmental fevers in the newborn period in the setting of other HLH findings should trigger a clinical suspicion of HLH after sepsis and other common causes have been ruled out.

One of the largest reviews of HLH in neonates was part of a 2009 case report of a twin pregnancy with fetal hydrops. (31) An extensive literature search from this review resulted in a total of 13 cases of HLH diagnosed prenatally or within the first week after birth. Significant findings included abnormal perforin and NK function, hepatosplenomegaly, cytopenias, and increased ferritin/fibrinogen in all 13 cases (1 twin died in the delivery room and testing was incomplete). In addition, 10 of 14 patients were male, 11 of 13 had respiratory issues requiring support, 10 had elevated bilirubin levels, 4 had fever, and 2 had hypothermia. Elevated liver function tests were noted in 12 patients with 1 unknown, coagulopathies were noted in 9 cases, and 7 patients had abnormal triglycerides. Only 4 fetuses developed hydrops between 28 and 36 weeks' gestation.

A 2009 case series also confirmed that hemophagocytosis is neither sensitive nor specific in diagnosing HLH. (39) Of the 14 neonatal cases, 8 had hemophagocytosis in the bone marrow, 4 had infiltration in the liver, 2 had splenic involvement, and 2 had hemophagocytosis in the placenta. Few of these neonates had biological testing, and sCD25/sIL-2R testing was available at the time of the report's publication. (31) Since then, several other case reports have been published about neonates with HLH with similar presentations.

As stated in numerous publications, the diagnosis of HLH is often camouflaged as other conditions commonly found in newborns. (22)(40)(41) Sepsis is a common consideration in the differential diagnosis (6)(22)(42) because both sepsis and HLH can present with characteristic multi-organ failure. (23)(41)(42) In older children, neurologic abnormalities and coagulopathies can be easily mistaken for a nonaccidental trauma. (43)(44)(45) Clinicians should consider HLH in their differential if a full diagnostic evaluation for child abuse is inconclusive.

An additional clinical consideration in the diagnosis of HLH is the presence of dermatologic abnormalities. Up to 65% of all patients with HLH in any age group will have some type of dermatologic finding. (34)(46)(47) Findings

may vary and the skin lesions are highly pleomorphic. These findings can range from a simple erythematous rash to conditions as complex as edema and purpura. (8)(48) The variations in skin presentation can often mimic common newborn rashes or exanthems, leading to a delayed diagnosis. (48) Physicians should consider HLH in infants with skin findings in the setting of other diagnostic criteria for HLH.

## MANAGEMENT

Once the diagnosis is confirmed, management should be aimed promptly at reducing the hyperinflammation and immune dysregulation. A delay in diagnosis and treatment results in increased mortality. (25) Clinicians should work closely with oncological services that are specialized in neonatal HLH at a care center that is equipped to administer treatment. Because most neonatal HLH cases are familial, allogeneic stem cell transplantation (SCT) is the only curative solution. (49) As such, HLA typing of the patient and search for an appropriate SCT donor should be conducted immediately. Therapy should be initiated based on Histocyte Society treatment protocols, such as HLH-94, or enrollment in a clinical trial may be considered while waiting for

**TABLE 2. Potential Medications for Use in Patients with Hemophagocytic Lymphohistiocytosis**

DRUG	DRUG CLASSIFICATION	MECHANISM OF ACTION	SIDE EFFECTS
Etoposide	Antineoplastic agent; topoisomerase II inhibitor	Causes breaks in DNA when interacting with the DNA/topoisomerase II complex, preventing further replication of DNA in late S and early G2 phase and inhibiting cell proliferation	Alopecia, nausea and vomiting, diarrhea, anorexia, leukopenia, thrombocytopenia, anemia, hypotension secondary to rapid infusion, hepatotoxicity, anaphylactoid reaction
Dexamethasone	Corticosteroid	Decreases inflammation by modulating the production of inflammatory mediators and suppressing neutrophil migration	Arrhythmia, embolism, hypertension, emotional lability, edema, hyperglycemia, hypokalemia, adrenal suppression, growth suppression, nausea and vomiting, increased appetite, increased serum transaminases, hypersensitivity
Cyclosporine A	Immunosuppressant; calcineurin inhibitor	Suppresses cell-mediated immune reactions by blocking transcription of cytokine genes in activated T cells	Hypertension, edema, headache, paresthesia, tremor, hypertrichosis, hirsutism, increased serum triglycerides, gingival hyperplasia, gastrointestinal upset, increased susceptibility to infection, renal insufficiency
Emapalumab	Monoclonal antibody	Inhibits interferon $\gamma$	Hypertension, tachycardia, irritability, skin rash, hypokalemia, appendicitis, constipation, abdominal pain, diarrhea, lymphocytosis, increased susceptibility to infection, infusion-related reaction, fever



an SCT donor. (50) Induction therapy consists of 8 weeks of chemotherapy including etoposide and dexamethasone with or without cyclosporine A. Intrathecal therapy is administered if there is central nervous system involvement. The primary goal of therapy is to maximize T-cell function while decreasing inflammation until SCT can be performed.

The antineoplastic etoposide is used to inhibit topoisomerase II, which is crucial for DNA replication and repair. Etoposide causes breaks in the DNA when interacting with the DNA/topoisomerase II complex, preventing further replication of DNA in the late S and early G<sub>2</sub> phases and inhibiting cell proliferation. (51) The glucocorticoid dexamethasone is used to decrease inflammation by modulating protein production intracellularly. (52) Cyclosporine A suppresses cell-mediated immune reactions by blocking transcription of cytokine genes in activated T cells. (53) Table 2 provides a summary of possible medications to use in patients with HLH.

Specific protocols for treatment failure, relapse, and remission should follow the 2004 Histiocyte Society HLH guidelines; clinicians are advised to work closely with an oncologist on long-term treatment plans after initial treatment.

In November 2018, the US Food and Drug Administration (FDA) approved emapalumab, a monoclonal antibody directed against interferon  $\gamma$  (IFN $\gamma$ ). Emapalumab is the first FDA-approved drug for HLH, specifically for the treatment of adult and pediatric patients with primary HLH that is refractory, recurrent, progressive, or intolerant to conventional therapy. (54) Mean age of all pediatric patients in the study at the time of diagnosis was 0.85 years and 79% lived to SCT. Although HLH is a hyperinflammatory disorder involving multiple cytokines, IFN $\gamma$ , specifically, has been found to play a pivotal role in disease activity. As a result, blocking IFN $\gamma$  was found to be effective in achieving responses in a clinical trial of emapalumab. (54)

## PROGNOSIS

As stated earlier, the only curative treatment for fHLH is hematopoietic SCT. Data are extremely limited, but children who achieved remission before transplantation did better than those who did not; even under optimal circumstances, the disease was often terminal. (55) With no intervention, the median survival is 2 months from the time of diagnosis. Multiorgan failure and systemic infection are the most common causes of mortality. (56) Because neonatal presentation of HLH is extremely rare, the outcomes data are limited and variable. Remission status, time

to transplantation, and other comorbid factors affect overall survival. Delay in control of disease with chemotherapeutic agents before transplantation has been shown to affect overall survival. (15)(32) Early diagnosis via genetic testing, treatment, and transplantation offer best chances for survival.

## CONCLUSION

Neonatal presentation of HLH is extremely rare. Clinicians should consider HLH in their differential diagnosis in neonates with unexplained fever, hepatosplenomegaly, and pancytopenia. Genetic testing should be considered if there is a clinical suspicion of HLH.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features and know the evaluation and management of disorders associated with T-cell dysfunction, including DiGeorge sequence and HIV infection.
- Know the initial screening tests and subsequent specific diagnostic tests used to evaluate neonates with possible defects in host defense mechanisms.

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1. Hemophagocytic lymphohistiocytosis (HLH) is a severe disorder that rarely presents in the neonatal period and can be defined as a hyperinflammatory syndrome of pathologic immune activation. HLH can be inherited (familial HLH [fHLH]) or acquired. Which of the following statements regarding the pathophysiology of fHLH is correct?
  - A. Genes identified as causes of HLH play a critical role in the initial steps of cytolytic granule secretion.
  - B. Mutations in the perforin gene (*PRF1*) on chromosome 10q22.1 represent the most commonly identified mutation, accounting for 60% of cases.
  - C. *STX11* and *BIRC4* are the only genes that have been associated with HLH in neonatal patients.
  - D. The majority of fHLH cases present after the first year of age.
  - E. *UNC13D* is the predominant mutation found in Hispanic patients.
2. HLH is associated with poor prognosis, emphasizing the need for early diagnosis and intervention in affected patients. The diagnostic criteria for HLH were initially published in 1999 by the Histiocyte Society and revised in 2004. Which of the following statements regarding the diagnosis of HLH is correct?
  - A. High natural killer cell activity is a diagnostic criterion for HLH.
  - B. Hypertriglyceridemia is the most helpful criterion in neonatal HLH.
  - C. Hyperferritinemia represents one of the criteria for the diagnosis of HLH.
  - D. The presence of low concentrations of soluble interleukin 2 receptor represents one of the criteria for the diagnosis of HLH.
  - E. There are 10 diagnostic criteria and the diagnosis of HLH can be established if at least 4 of these criteria are present.
3. The clinical manifestations of HLH are variable and can be mistaken for other common disorders. Which of the following statements regarding the clinical presentation of HLH is correct?
  - A. An elevated ferritin level is an uncommon finding in neonates with HLH.
  - B. Dermatologic abnormalities are uncommon at the time of presentation.
  - C. Hyperthermia is the most common presenting symptom in both neonates and older infants.
  - D. In children younger than 15 years, the most common clinical signs include fever, hepatosplenomegaly, and coagulopathies.
  - E. In neonates, hydrops and elevated transaminases represent the most common findings.
4. A prompt diagnosis of HLH in affected neonates is critical to initiate therapies aimed at reducing inflammation and immune dysregulation, and decrease mortality. Which of the following statements regarding the management of HLH is false?
  - A. Allogeneic stem cell transplantation is the only curative solution.
  - B. Cyclosporine A can be used to block transcription of cytokine genes in activated T cells and suppress cell-mediated immune reactions.
  - C. Dexamethasone can be used to modulate intracellular protein production and decrease inflammation.
  - D. Emapalumab, a monoclonal antibody directed against interferon  $\gamma$ , was recently approved for the treatment of adult and pediatric patients with primary refractory HLH.
  - E. Etoposide is used to inhibit topoisomerase I, thereby causing breaks in the DNA and inhibiting cell proliferation.

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5. Since November 2018, emapalumab has been approved by the US Food and Drug Administration, and is specifically targeted at primary HLH that is refractory, recurrent, progressive, or intolerant to conventional therapy. Of the following, the purported mechanism of action of emapalumab in modulating disease activity is:
- A. As a competing agonist toward complement.
  - B. As a monoclonal antibody directed against and blocking interferon  $\gamma$ .
  - C. Binding to signaling proteins in B and T cells.
  - D. By increasing the production of several coagulation factors in the liver.
  - E. By stimulating erythropoiesis as well as other cell lines in the bone marrow.
-

## Neonatal Hemophagocytic Lymphohistiocytosis

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# Severe Combined Immunodeficiency: A Review for Neonatal Clinicians

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## Education Gaps

1. Pediatric clinicians should be able to describe the normal development and function of lymphocytes along with how neonatal immunity varies from that of adults and older children.
2. Neonatal clinicians should be proficient in the diagnosis and initial management of infants suspected of having a severe combined immunodeficiency.

## Abstract

The proper development and function of T cells is imperative in the creation of adequate cell-mediated and humoral immunity. Healthy term newborns have baseline immune immaturity, increasing their risk of infections, but significant immunologic consequences can occur, because of abnormal T-cell maturation. Combined immunodeficiencies can result, because B cells and natural killer cells rely on successful interactions with T cells to ensure their proper performance and survival. Severe combined immunodeficiency (SCID) is the most noteworthy of these conditions, leading to considerable early morbidity and often death by the age of 1 year if left untreated. Newborn screening for SCID is effective and allows for early implementation of lifesaving supportive measures, including protective isolation, initiation of prophylactic antimicrobials, caution with blood product transfusions, and avoidance of live vaccinations. Once a definitive diagnosis of SCID has been established, treatment frequently involves bone marrow or stem cell transplantation; however, enzyme replacement and gene therapy are also becoming options in those with SCID due to adenosine deaminase deficiency and other forms of SCID. Neonatal clinicians should understand the screening and diagnostic approach to SCID along with the initial management approaches for these extremely high-risk patients.

**AUTHOR DISCLOSURE** Drs Michniacki, Seth, and Secord have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

ADA	adenosine deaminase
APC	antigen-presenting cell
HSCT	hematopoietic stem cell transplantation
MHC	major histocompatibility complex
NBS	newborn screening
NK	natural killer
SCID	severe combined immunodeficiency
TRECs	T-cell receptor excision circles

## Objectives After completing this article, readers should be able to:

1. Explain the normal development and function of lymphocytes and describe how they interact to successfully enable innate and adaptive immunity.

2. Describe newborn immunity with an emphasis on neonatal cell-mediated and humoral immunity.
3. Explain the pathophysiology, clinical presentation, and diagnosis of severe combined immunodeficiency and related conditions.
4. Recognize the benefits and limitations of newborn screening for severe combined immunodeficiency.
5. Successfully implement the initial management strategies in an infant suspected to have severe combined immunodeficiency.
6. List the various treatment modalities for a patient with severe combined immunodeficiency and related conditions.

## INTRODUCTION

In this review, we provide a summary of severe combined immunodeficiency (SCID) and related conditions with additional education on the normal development and function of lymphocytes, with an emphasis on neonatal immunology. Educating neonatal clinicians about screening, confirmatory diagnostic, and initial management approaches for newborns with disorders of cellular immunity, including SCID, is imperative to ensuring optimal outcomes for these high-risk patients.

## NORMAL DEVELOPMENT AND FUNCTION OF LYMPHOCYTES AND IMMUNITY IN THE NEONATE

Hematopoietic stem cells give rise to all cellular blood components, including lymphocytes, which develop after a pluripotent stem cell's transition to the common lymphoid progenitor. This progenitor may then progress to 1 of 3 lineages: B cells, T cells, or natural killer (NK) cells. T cells and B cells are involved in the body's adaptive immune response through cell-mediated immunity (facilitated by T cells) and humoral immunity (mediated by B cells). NK cells act as a major component of innate immunity. (1)

Precursor B cells initially develop predominantly in the bone marrow before transition to the spleen and lymph node germinal centers. It is in the germinal centers that mature B cells (expressing CD19, CD20, IgM, and IgD surface markers) either become plasma cells that secrete protective immunoglobulins or memory B cells (expressing IgG, IgA, or IgE surface markers) that assist in the secondary immune response. By recognizing and binding to specific antigens, immunoglobulins assist in the eventual destruction of harmful pathogens. (1) Immunoglobulin production, especially IgG, in the fetus is poor, given

minimal plasma cell differentiation and a lack of significant immunoglobulin isotype class switching. Fortunately, term infants are afforded some assistance with immunity via the placental transfer of maternal IgG that begins around 32 weeks' gestation. Premature infants born before 32 weeks' gestation thus have profound IgG deficiency. Maternal IgG will allow for sufficient humoral protection in the term infant until approximately 6 months of age. Specific antibody production becomes adequate for some protein antigens by 2 months of age and is delayed for polysaccharide antigens until approximately 24 months of age. (2)

Commitment of the common lymphoid progenitor to a T lineage and proper development and function of T lymphocytes requires stem cell passage through the thymus. It is in the thymus that the T-cell receptor is first expressed on the cell surface. Initially, the double-negative (CD4<sup>-</sup> CD8<sup>-</sup>) thymocytes upregulate both CD4 and CD8 to become double-positive (CD4<sup>+</sup> CD8<sup>+</sup>) cells. (1) During the process of positive and negative selection, either CD4 or CD8 is suppressed, creating helper or cytotoxic T cells, respectively. CD8<sup>+</sup> cells are involved in cell lysis whereas CD4<sup>+</sup> cells assist CD8<sup>+</sup> cells in the cellular lytic process and also interact with B cells via soluble factors and direct cell-to-cell communication to produce antibodies. (1) As a result of this B-cell functional dependence on T cells, qualitative or quantitative T-lymphocyte defects will often cause B-cell deficiency or poor humoral immunity. (3) In addition to the helper and cytotoxic varieties, T cells eventually develop into effector, memory, and regulatory subtypes to complete the impressive functionality of T lymphocytes. Antigen specificity and effective adaptive immunity is created through somatic rearrangements of T-cell receptor genes to create a diverse population of T lymphocytes. Successful adaptive immunity also requires the activation of naïve T

cells, which involves not only an interaction between the T-cell receptor and major histocompatibility complex (MHC) on antigen-presenting cells (APCs) but also the binding of various T-cell surface molecules to additional ligands present on APCs (costimulation). Cytokines play a crucial role in T-cell activation, with interleukin 2 leading to a sustained proliferation of lymphocytes. (1)

Fetuses and newborns have an increased vulnerability to pathogens that require T cells for optimal control, such as viruses, fungi, parasites, and mycobacteria. Unlike humoral immunity, infants do not receive passive maternal T-cell immunity assistance during gestation and thus must rely on their own autologous T cells for protection. It is hypothesized that this elevated infectious sensitivity found in neonates is partially secondary to decreased differentiation of neonatal naïve CD4 T cells and relative APC immaturity, especially dendritic cells. (2)

NK cells are considered innate lymphoid cells that function as cytotoxic cells with a primary role of destroying cells infected with viruses and intracellular bacteria. Cytokines and antibodies (via coating of pathogen-inflicted cells) enhance and assist in the NK cell process of cellular destruction. In addition, NK cells produce interferon  $\gamma$ , which activates macrophages. (4) NK cells develop from the common lymphoid progenitor cell and do not require thymic maturation. (1)

## SCID AND OTHER COMBINED IMMUNODEFICIENCIES

SCID refers to a heterogeneous group of disorders with deficits in T-cell immunity, often leading to additional impairment of B-cell function and sometimes NK-cell dysfunction. The deficits are usually in the immune system, but in some cases, are from enzyme deficiencies affecting immunity. In all cases, the lack of cell-mediated and humoral immunity in these patients leads to overwhelming infections and death, typically by 1 year of age if left untreated. (1)(5) The overall incidence of SCID, after initiation of newborn screening (NBS), has been found to be 1 in 58,000 births with a higher incidence found in the Navajo Nation (1 in 3,500 births) because of a founder mutation in *DCLRE1C* in this population. Before routine NBS became common, the incidence was often cited as 1 in 200,000, highlighting the fact that many cases were missed before routine screening. (6) Infants with SCID who were missed before NBS became commonplace died before diagnosis. (7)

Criteria to meet the diagnosis of typical SCID include an absence or extremely low absolute number of T cells ( $<300$  CD3 T cells/mm<sup>3</sup>) and very low T-cell functionality ( $<10\%$  of lower limit of normal) found on mitogen stimulation

assessment. Patients may also show low B-cell and NK-cell absolute values and decreased quantitative immunoglobulin levels, though these findings are not required for diagnosis. Leaky SCID refers to a combined immunodeficiency caused by a hypomorphic mutation in a recognized SCID-causing gene, leading to the production of some T cells (typical levels of 300–1,500 cells/ $\mu$ L) that are poorly functioning (mitogen stimulation of 10%–30% of normal controls). (5)(8) Maternal engraftment of T cells can occur in infants with SCID, given a lack of autologously produced fetal T cells to eliminate placentally transferred lymphocytes. These cells typically will fail to respond to mitogen stimulation but may cause graft-versus-host disease in the neonate, manifesting as cutaneous and hepatic abnormalities. (1)(5)(9) Clinicians should be aware of the phenomenon of Omenn syndrome in those with leaky SCID. The syndrome is thought to result from the clonal proliferation of a population of T lymphocytes present in the patient with leaky SCID. These infants may present with normal lymphocyte numbers and a response to mitogen stimulation but continue to have poor immunologic function, leading to immunodeficiency in the neonate. Despite immune dysfunction, patients will present with signs and symptoms of excessive inflammation, including lymphadenopathy, hepatosplenomegaly with transaminitis, erythematous rash, eosinophilia, and IgE elevation. Treatment specifics of Omenn syndrome are beyond the scope of this review, but many patients require immunosuppressive therapy to control their deleterious inflammation. (5)(10)

Categorization of typical SCID according to the 2017 International Union of Immunological Societies' primary immunodeficiency expert committee is based on the type of peripheral lymphocyte impairment and specific molecular derangement, leading to lymphocyte dysfunction in a patient (Table). (11) Adenosine deaminase (ADA)-deficient SCID is especially noteworthy because it causes accelerated lymphocyte apoptosis secondary to the build-up of metabolites in the salvage pathway of purine nucleoside synthesis due to the absence of the ADA enzyme. (1) Molecular abnormalities in the *IL2RG*, *IL7R*, *ADA*, *RAG1*, and *JAK3* genes appear to be the most commonly identified SCID aberrations. (6) Mutations leading to purine nucleoside phosphorylase (*PNP*), Zeta chain-associated protein kinase 70 (*ZAP70*), MHC class I/II, and dedicator of cytokinesis 8 (*DOCK8*) deficiencies are not considered classic SCID conditions but may still cause profound combined immunodeficiency. Complete DiGeorge syndrome can also present with significant cell-mediated and humoral immunity difficulties, given a thymus that is absent or severely hypoplastic. (1)(5)

**TABLE. Classification of the Causes of Severe Combined Immunodeficiency**

LYMPHOCYTE IMPAIRMENTS	MOLECULAR DEFECT
T- B+ NK-	<i>IL2RG, JAK3</i>
T- B+ NK+	<i>IL7R, CD3D, CD3E, CD247, PTPRC, CORO1A, FOXP1</i>
T- B- NK-	<i>ADA, AK2</i>
T- B- NK+	<i>LIG4, NHEJ1, PRKDC, RAG1/RAG2, DCLRE1C (Artemis)</i>

Classification system is recommended by the 2017 IUUIS Primary Immunodeficiency Expert Committee. ADA=adenosine deaminase, AK2=adenylate kinase 2 (reticular dysgenesis), CD=cluster of differentiation, CD3D=CD3δ, CD3E=CD3ε, CORO1A=Coronin 1A, DCLRE1C=DNA cross-link repair enzyme 1C, FOXP1=Forkhead box N1, IL2RG=interleukin 2 receptor common γ chain, IL7R=interleukin 7 receptor, IUUIS=International Union of Immunological Societies, JAK3=Janus kinase 3, LIG4=DNA ligase IV, NHEJ1=nonhomologous end-joining protein 1, PRKDC=DNA-dependent protein kinase, PTPRC=protein tyrosine phosphatase receptor type C, RAG=recombinase activating gene.

Infants with SCID may have a family history of a known primary immunodeficiency or early infant death secondary to infection or an unknown cause. Most newborns with SCID will appear normal without any specific abnormalities at birth, but if not detected on NBS, a diagnosis should be suspected in those who develop failure to thrive, chronic diarrhea, recurrent fevers/infections, persistent mucocutaneous candidiasis, or infections with atypical pathogens including mycobacteria, *Cryptosporidium*, and *Pneumocystis jirovecii*. (1)(3)(5)(12) Despite the relatively rare occurrence of SCID and other combined immunodeficiencies, the neonatal clinician should have an elevated index of suspicion for these conditions given their high morbidity and mortality.

## NEWBORN SCREENING FOR SCID

In 2010, the United States Department of Health and Human Services recommended uniform screening for SCID in all newborns. NBS is recommended for disorders that are life-threatening, have a screening test with reasonable sensitivity and specificity, and have a treatment available to improve outcome. SCID is undoubtedly an acceptable condition for widespread screening given that testing for the detection of T-cell receptor excision circles (TRECs) is not only sensitive and specific but has a relatively low cost and the ability to readily detect presymptomatic infants, allowing for effective treatment interventions. (13) As of 2018, 47 states included SCID in their NBS programs,

with Alabama, Indiana, and Louisiana moving toward implementing SCID detection methods at birth. (14)

Diagnosis of SCID at birth via NBS allows for protective measures to be undertaken to decrease the risk of infection in the infant. If necessary, a diagnosis will allow the neonatal clinician to initiate an immediate evaluation for hematopoietic stem cell transplantation (HSCT); early transplantation, especially before age 6 months and before any infection develops in the infant, is associated with improved outcomes. (15) This survival benefit after HSCT following an early diagnosis of SCID is substantial, regardless of donor match, transplant conditioning method, or SCID type. (16) Early detection also allows enzyme replacement therapy to begin as soon as possible in those with SCID secondary to ADA deficiency who lack a suitable transplant donor or require bridging therapy before transplantation. (17)

Given the genetic heterogeneity of SCID, an NBS method was developed that detects the common disease phenotype of impaired T-cell immunity. (18) The technique relies on detecting the presence of DNA fragments produced via gene rearrangements during the creation of a diverse T-cell population capable of recognizing an assortment of antigens. Genes necessary for the creation of variable T-cell receptors undergo splicing in thymocytes, resulting in excised DNA fragments that are not integrated into the final receptor gene product, and forming round byproducts called TRECs. TRECs do not replicate during mitosis and thus are most prominent in naïve T cells that have not undergone extensive proliferative cycles. Polymerase chain reaction allows for detection of TRECs with a low number raising concern for either poor autologous T-cell production or increased loss of peripheral blood T cells. As a result, the test detects not only SCID, but any condition associated with insufficient T-cell numbers. (18) In addition, the assay will identify infants with SCID with either maternal engraftment of T cells or Omenn syndrome, given that these conditions arise from activated memory T cells, which do not contain significant TRECs. (19)

In the original pilot study assessing TRECs as a screening tool for SCID, healthy term neonates were found to have TREC levels greater than 1,000 in two 3-mm punches obtained from NBS cards whereas infants with SCID had levels of nearly zero (values <30). (20) This substantial difference between healthy infants and those with SCID makes TREC analysis an excellent screening test. It must be noted that there is great variability among state screening programs with respect to TREC level cutoffs that lead to a positive result and referral of a patient for further testing. The rates of false-positive results, therefore, vary by state. (6) Despite these varying cutoffs, an extensive systematic review of TREC-based NBS showed the sensitivity of detection for typical SCID to be 100%. (21)

An important educational point is that T-cell lymphopenia secondary to delayed-onset ADA-SCID may be missed through TREC screening but can be detected with tandem mass spectrometry or the  $\kappa$ -deleting recombination excision circles assay, which identifies B-cell deficits through a similar methodology as TRECs but via genetic rearrangements occurring during light and heavy chain production. (19)(21)(22) Tandem mass spectrometry has long been used in NBS to detect classic conditions of inborn errors of metabolism, including phenylketonuria and homocystinuria; however only recently has it been recognized and implemented to identify cases of both ADA and PNP-deficient combined immunodeficiencies. (23)(24) It is likely that NBS programs will continue to expand to improve the detection of delayed-onset ADA-SCID, because studies have shown that doing so is not only relatively simple but also cost-effective. (25)(26) Additional conditions with T-cell impairment, such as ZAP70 deficiency and MHC class II deficiency, may also not be revealed through standard TREC testing given that in these disorders, T-cell dysfunction occurs after the production of TRECs in lymphocytes. (18)(27)

Infant prematurity may lead to low TREC values and eventually false-positive results. Furthermore, the frequent exposure of premature infants to corticosteroids and the lack of age-matched reference values for T-cell and B-cell subset flow cytometry analyses obtained in preterm neonates causes difficulties in data interpretation while determining the validity of a low TREC number. Preterm infants are often retested until a normal result is obtained or on reaching a gestational age of 37 weeks or greater. Such retesting ensures that the initial testing abnormalities were indeed caused by prematurity and not true immunodeficiency, which could also occur in a preterm neonate. (28)(29)

Despite its imperfections, TREC screening unquestionably has been successful in improving the clinical outcomes and survival of infants suffering from SCID while also identifying additional at-risk neonates presenting with significant T-cell lymphopenia or impairment. We are hopeful that NBS methodology continues to improve and decrease the false-positive and false-negative rates while ensuring excellent sensitivity, specificity, and cost-effectiveness of testing. (30)

## MANAGEMENT OF SUSPECTED COMBINED IMMUNODEFICIENCY IN AN INFANT

A clinician may suspect a primary immunodeficiency condition in a neonate based on clinical history, family history, or physical examination findings. An abnormal TREC screening result may also lead to further investigation by the pediatrician or neonatologist. A low TREC value

should prompt consideration for not only SCID but additional conditions associated with low circulating naïve T cells, including trisomy 21, DiGeorge syndrome, ataxia telangiectasia, trisomy 18, and CHARGE syndrome (coloboma, heart defects, atresia of nasal choanae, growth restriction, genital or urinary anomalies, and ear abnormalities or deafness). Nonimmunologic disorders with associated immune deficiency, such as cartilage hair hypoplasia, also can be discovered on TREC screening. Conditions leading to secondary T-cell lymphopenia detected via screening include congenital cardiac conditions (as a result of surgery or vascular leak causing third spacing of lymphocytes), chylous effusions, gastrointestinal anomalies, and neonatal leukemia. (6)(18) Reassuringly, a substantial analysis of data related to NBS for SCID via the TREC assay revealed that most infants with an abnormal TREC screen actually do not have persistent T-cell lymphopenia on follow-up testing, and only a minority of infants with T-cell lymphopenia actually have SCID. (31) Despite this fact, a low TREC value should lead to prompt notification of the family, pediatrician, and a clinician/local institution with expertise in the care and management of combined immunodeficiencies. TREC testing should be repeated after any abnormal or inconclusive result. The initial sample should also have verification that it contained an adequate amount of quality DNA by using a polymerase chain reaction control consisting of primers amplifying unrelated genomic DNA (usually the *RNaseP* or  *$\beta$ -actin* genes). (18)

After verification of a low TREC value, additional qualitative and quantitative immunologic testing should be undertaken. The distribution and absolute values of T-cell, B-cell, and NK-cell subsets via flow cytometry should be undertaken with analysis of naïve (CD45RA+ CD62L+) and memory (CD45RO+ CD62L-) T lymphocytes included in the panel to identify patients with leaky SCID or maternal T-cell engraftment. A newborn is expected to have a preponderance of naïve T cells; a preponderance of memory cells is suspicious for maternal engraftment.

Mitogen proliferation studies allow for functional testing of lymphocytes, and B-cell maturation panels detect varying subsets of maturing B cells. IgM, IgG, IgE, and IgA levels should be obtained to evaluate humoral immunity. In older infants already exposed to vaccinations or when infections have already occurred, appropriate antibody production capabilities can be assessed, but care must be taken to evaluate for the presence of passive maternal IgG antibodies versus the infant's own production of antibody. (1)(3)(6)(19) Testing for disease-causing mutations may lead to a molecular diagnosis but the implementation of widespread NBS has resulted in the identification of an ever-increasing



number of infants who are found to have idiopathic T-cell lymphopenia without an identifiable genetic cause. (1)(6)(18) Infants with continued T-cell lymphopenia without a definitive genetic cause may still be at risk for serious infections, yet no consensus has been established for the standard management of these conditions.

Imaging may also be of assistance in diagnosis because the absence of a thymic shadow on chest radiography could possibly be a clue to a significant underlying immunodeficiency. However, the practitioner must recognize that early thymic involution may also occur in the setting of corticosteroid exposure or at times of high stress, including after trauma, infection, or respiratory distress. (32) Hypoplasia of additional lymphatic tissue, including peripheral lymph nodes and tonsils, may be found in patients with SCID, though even healthy newborns initially do not normally show prominent tonsils or adenoids. (12)

In those definitively diagnosed with a combined immunodeficiency, protective isolation measures must be undertaken to limit exposure to infectious agents. Intravenous immunoglobulin therapy should be given to maintain an IgG trough level of 500 to 800 mg/dL (5–8 g/L). The monoclonal antibody palivizumab should be given to at-risk infants during the respiratory syncytial virus season. Prophylaxis against fungal organisms with fluconazole is recommended with an additional low threshold to begin broad-spectrum antimicrobials in those with a suspected bacterial infection. Herpesvirus family (ie, herpes simplex virus, cytomegalovirus and Epstein-Barr virus) and *P jiroveci* prophylaxis should be started with acyclovir and trimethoprim-sulfamethoxazole, respectively. Trimethoprim-sulfamethoxazole can be safely administered as early as 1 week after birth, provided hepatic function is monitored closely with intravenous pentamidine as an alternative *P jiroveci* prophylaxis agent if there is concern for hepatotoxicity. (1)(3)(33)(34) Blood products must be limited to those that are cytomegalovirus-negative, leukoreduced, and irradiated. Transfusion with blood products containing viable lymphocytes may lead to fatal transfusion-related graft-versus-host disease. Vaccines are not effective in these infants with no ability to respond and should not be given; however, live vaccines, including the rotavirus immunization, should especially be avoided because they may lead to life-threatening active infections. (6)(18)(34)

## DEFINITIVE TREATMENT OF SCID AND RELATED CONDITIONS

In infants with SCID, the phenotypic severity of the disorder necessitates definitive treatment aimed at resolving the

significant immunologic dysfunction. For most patients with genetically verified SCID or T-cell lymphopenia causing serious consequences, allogeneic HSCT is the preferred treatment modality. (1)(5)(11)(35) The 2-year survival rates after transplantation in patients with SCID are now 90% for all patients and 95% if the infant was infection-free at the time of transplantation. (36) ADA-SCID uniquely has additional treatment options because of the fact that an enzymatic abnormality underlies its pathophysiology. In addition to HSCT, patients with ADA-SCID may receive enzyme replacement therapy or autologous HSCT with gene therapy. Allogeneic transplantation is still preferred in those with a matched family donor with additional consideration for enzyme replacement therapy as well if some endogenous immunity is required to fight an infection or if pulmonary alveolar proteinosis is suspected before transplantation. (17)(35) Enzyme therapy may be successfully used in patients with ADA-SCID without an appropriate HSCT donor option or as a bridge to autologous transplantation with gene therapy. (16)(37) With gene therapy, a functional copy of the ADA gene in a viral vector is transduced into hematopoietic stem cells and then infused into the patient. (1)(17) This treatment method, which is currently only available outside of clinical trial use in Europe, has shown success in patients with ADA-SCID without the subsequent development of treatment-related leukemia via insertional mutagenesis in an oncogene as was noted in patients with SCID with the *IL2RG* gene who had been previously treated with gene therapy. (5)(17)(38)(39)(40)(41) Recently completed and actively enrolling clinical trials analyzing the safety and efficacy of various modified gene therapy methods for ADA, Artemis deficiency, and X-linked SCID will hopefully soon be approved in the United States. (42)(43)(44)(45)(46)(47)(48) Interestingly, thymus transplantation in those with congenital athymia, such as patients with DiGeorge syndrome, can result in impressive immune reconstitution. (49) HSCT for complete DiGeorge syndrome is associated with relatively poor survival, likely because of the frequent occurrence of severe graft-versus-host disease and continued lack of thymic function, making transplant recipients unable to generate T cells against novel pathogens. (5)(50)

## CONCLUSION

With early diagnosis via NBS and subsequent proper initial management provided by the neonatal clinician, most combined immunodeficiencies, including SCID, have transitioned from disorders that once presented with high morbidity and mortality to conditions that can be successfully treated with excellent outcomes. Neonatal clinicians are



at the frontline of safety for these extremely vulnerable infants. We hope this review will give readers a better understanding of the pathophysiology and treatment recommendations for this immunodeficient patient population.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the timing and developmental stages of lymphoid tissues in the neonate and infant.
- Know the two types of host defense mechanisms (innate and acquired immunity) and understand their role and interrelationship in normal development of the immune system.
- Know the normal immunoglobulin patterns in preterm and full-term newborn infants.
- Know the activation and function of B-lymphocytes.
- Know the function of immunoglobulins.
- Know the mechanisms and gestational timing of the placental transfer of immunoglobulins.
- Know the laboratory methods for diagnosing immune deficiencies.
- Know the development and function of T-lymphocytes.
- Know the function and activation of T-lymphocytes, including the role of cytokines.
- Recognize the clinical features and know the evaluation and management of disorders associated with T-cell dysfunction.

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1. Preterm infants are particularly vulnerable to infections and the role of the mother in facilitating transition from intrauterine to extrauterine life includes providing immune protection. Which of the following statements regarding immunoglobulin transfer to the neonate is correct?
  - A. Maternal IgG transferred to the infant via the placenta and breast milk will last for up to 4 years.
  - B. Placental transfer of maternal IgG begins around 32 weeks' gestational age.
  - C. Most of the maternal IgG and IgA transfer occurs right at the time of delivery through delayed cord clamping.
  - D. The preterm infant will begin antibody production, with noticeable increase in IgG levels several hours after birth and specific antibody production becoming adequate for most protein antigens by 1 week of age.
  - E. The sole source of immunoglobulins for term infants is that provided via maternal breast milk.
2. T lymphocytes develop and differentiate in the thymus. Infants do not receive passive maternal T-cell immunity during gestation and must rely on their own autologous T cells for protection. Which of the following statements regarding T lymphocytes is correct?
  - A. A deficiency in T-cell numbers or function will usually lead to compensation by B cells to increase in number and activity.
  - B. CD4+ CD8+ cells are the most common final pathway for most neonatal T cells.
  - C. CD4+ cells are produced by plasma cells.
  - D. CD4+ cells inhibit the action of CD8+ cells in foreign cell destruction.
  - E. CD8+ T cells are involved in cell lysis.
3. A 1-month-old infant has had persistent mucocutaneous candidiasis despite treatment. Family history includes early infant death in a sibling after infection. Severe combined immunodeficiency (SCID) is suspected. Which of the following statements concerning SCID is correct?
  - A. Maternal engraftment of T cells by total body exchange transfusion is a treatment strategy that has an approximately 50% success rate.
  - B. Most neonates with SCID have an acute presentation during the first few days after delivery, with circulatory shock and overwhelming sepsis, usually with group B *Streptococcus*.
  - C. SCID is a specific disorder characterized by a mutation in the *SNK1* gene which leads to an inability to produce natural killer cells.
  - D. The incidence in the general population is approximately 1 in 10,000 live births.
  - E. Typical or classic SCID is characterized by absence or extremely low absolute number of T cells and very low T-cell functionality found with mitogen stimulation assessment.

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4. Newborn screening for SCID has become widespread. Which of the following statements regarding newborn screening for SCID is correct?
- A. A rationale for screening and early diagnosis is that early hematopoietic stem cell transplantation, particularly before age 6 months and before any infection develops, is associated with improved outcomes.
  - B. Because of the robust immune response in the first 2 days after preterm birth, the screening result in preterm infants with SCID is usually negative. Therefore, there is high positive predictive value and large numbers of false-negative tests.
  - C. The most common newborn screening test used for SCID detects a mutation in the *SNK1* gene.
  - D. The primary role of screening is for counseling, because no actual medical treatments are available at this time for any diagnosis of SCID.
  - E. Although newborn screening has good positive predictive value for SCID, no current tests can detect other conditions that may have insufficient T-cell numbers.
5. An infant has a positive newborn screening result for SCID. The test is based on detection of T-cell receptor excision circles. Which of the following would be an appropriate next step for this infant?
- A. An initial positive screening result should prompt admission to a negative pressure isolation room in the NICU.
  - B. Among term infants with a positive screening result with this method, approximately 75% will be diagnosed with SCID.
  - C. The most important laboratory test that should be performed after initial positive screening is a blood culture.
  - D. Not only SCID, but also other conditions should be considered, such as trisomy 21, DiGeorge syndrome, trisomy 18, and CHARGE syndrome.
  - E. Transfusion of whole blood in the first week and then on a monthly basis can provide lymphocytes that will help to reduce infection risk for the first year.

## Severe Combined Immunodeficiency: A Review for Neonatal Clinicians

Thomas F. Michniacki, Divya Seth and Elizabeth Secord

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# Hematopoietic Stem Cell Transplantation: A Neonatal Perspective

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## Education Gaps

Allogeneic hematopoietic stem cell transplantation is often the only therapy that can control disease-related complications in many serious disorders of infancy and early childhood. Recognition of indications, timing, and the approach to transplantation in these nonmalignant disorders vary based on individual diagnoses. For example, in some conditions, the best outcomes are achieved when transplantation is undertaken before the onset of clinical symptoms or organ complications. This review provides an overview of transplantation from the neonatology perspective.

## Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) is indicated in various nonmalignant disorders that arise from genetic, hematopoietic, and immune system defects. Many of the disorders described here have life-threatening consequences in the absence of HSCT, a curative intervention. However, timing and approach to HSCT vary by disorder and optimum results are achieved by performing transplantation before irreversible disease-related morbidity or infectious complications. This article details the principles of HSCT in the very young, lists indications, and explores the factors that contribute to successful outcomes based on transplantation and disease-related nuances. It provides an overview into the HSCT realm from a neonatologist's perspective, describes the current status of transplantation for relevant disorders of infancy, and provides a glimpse into future efforts at improving on current success.

## Objectives

After completing this article, readers should be able to:

1. Describe nonmalignant disorders of infancy that can be modified or cured with hematopoietic stem cell transplantation.
2. Recognize neonatal disorders that require emergent referral for transplantation.

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## ABBREVIATIONS

AML	acute myeloid leukemia
ANC	absolute neutrophil count
CAMT	congenital amegakaryocytic thrombocytopenia
fHLH	familial (or primary) hemophagocytic lymphohistiocytosis
GALC	galactocerebrosidase
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
HLA	human leukocyte antigens
HSCT	hematopoietic stem cell transplantation
IMO	infantile malignant osteopetrosis
IPEX	immune dysregulation, polyendocrinopathy, enteropathy X-linked
MDS	myelodysplastic syndrome
MHC	major histocompatibility complex
NK	natural killer
NMA	nonmyeloablative
NMD	nonmalignant disorders
RIC	reduced intensity conditioning
SCID	severe combined immunodeficiency disorder
SCN	severe congenital neutropenia

### 3. Explain the principles of transplantation in infancy such as donor source, conditioning, outcomes, and long-term follow-up.

## INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) can serve as curative therapy for many nonmalignant disorders (NMD) of infancy and early childhood. Most of these disorders can be classified under the following broad categories: immunodeficiency, immune dysregulation, inherited genetic disorders, and bone marrow failure syndromes. The goal of this article is to provide an overview of the key principles of HSCT in infancy including donor choice, recipient/disease considerations, conditioning regimens and transplantation methods, and toxic effects of therapy including late sequelae.

The process of allogeneic HSCT was initially developed to replace the hematopoietic system as a treatment for malignant disorders such as leukemia. However, HSCT can replace hematopoietic and immune systems in children with NMD affecting these systems, using donor-derived cells. Donor pluripotent cells can also migrate to organs such as the bone or the brain, supplying deficient cells and enzymes in many neonatal disorders. Therefore HSCT benefits recipients with NMD by supplementing or replacing deficiencies in normal products of hematopoiesis, metabolism, or immune function. Although an asymptomatic donor with a trait (eg, thalassemia) is acceptable and capable of reversing disease manifestations in some disorders, this genetic manifestation in a donor is less desirable in other disorders such as mucopolysaccharidosis, in which low enzyme levels supplied by a trait donor may be incapable of reversing disease manifestations. The efficiency of disease control is also variable and disease dependent. Disease reversal is complete and efficient, irrespective of timing in some disorders such as marrow failure syndromes (provided there was no progression to clonal hematopoietic proliferation); however, speed is of essence in other diseases such as metabolic disorders that affect growth or neurologic function. These aspects will be discussed further under individual disorders.

The benefits and timing of HSCT should be considered in the context of age and disease-related morbidity, especially in the very young. HSCT has inherent toxicities associated with conditioning regimens that use a combination of chemotherapy and immune suppression, graft failure, graft-versus-host disease (GVHD), and immune deficiency until reconstitution. Transplantation studies are directed at optimizing donor selection, timing, and transplantation methods

to derive maximum benefit against the NMD with minimal toxicity, and early recovery.

## DONOR SELECTION

The primary source of allogenicity is determined by a set of cell surface proteins called human leukocyte antigens (HLA) encoded on chromosome 6 and genetically transmitted. These antigens form the major histocompatibility complex (MHC) in humans. HLA-A, -B and -C antigens belong to the class I system, and the MHC complex and the peptides they bind are recognized as self or nonself (allogeneic) by CD8 T cells. HLA-DR, -DQ and -DP antigens belong to the MHC class II system and are recognized in a similar fashion by CD4 T cells, eliciting an allogeneic response. The degree of donor and recipient matching thus drives GVHD with target organ damage in the recipient and host-versus-graft response responsible for graft rejection. Both of these are unfavorable toxic effects of transplantation and are inversely proportional to the degree of HLA matching between the donor and recipient. The most important HLA antigens involved in graft and host responses are HLA-A, -B, -C and -DRB1; the set totals 8 antigens that drive donor-recipient matching, though matching at additional “minor” loci can further improve outcomes. Matching rules naturally select fully HLA-matched siblings as the best donors in the absence of disease and when relevant, the trait. Matched family members other than siblings are rare except in closed ethnic communities. Alternate donor sources include registries of voluntary donors and cord blood products cryopreserved in cord blood banks, maintained through registries (eg, the National Marrow Donor Program in the United States). More recently, haploidentical family members have been used in increasing numbers because modern transplantation techniques allow for acceptable rejection rates and GVHD risks. HLA matching generally tracks with ethnicity; based on numbers of voluntary donors, minority races have a smaller chance of finding matched donors in the registry compared with white patients. (1)

Stem cell sources include bone marrow (harvested in the operating room), growth factor-mobilized peripheral blood stem cells, and umbilical cord blood products cryopreserved in cord blood banks. Stem cell sources are important in that umbilical cord blood requires more intense conditioning to

engraft (likely because of the immaturity and low cell dose) and has delayed engraftment but lower chronic GVHD rates. Cord blood is particularly attractive for HSCT in infants because mismatched cord transplantations have similar outcomes as HLA-matched marrow HSCT, and cell dose is likely to be adequate given the small size of the recipient. More recently, multiple techniques have shown promise in successfully expanding cord blood in vitro and are expected to enhance cord blood use. Peripheral blood that has not been manipulated has higher rates of GVHD likely because of a large T-cell load from the donor.

## CONDITIONING THERAPY

Conditioning therapy refers to agents administered to the recipient before transplantation to support engraftment of donor cells. The standard approach to conditioning is chemotherapy and/or radiation therapy, which is administered to transplant recipients before stem cell infusion. In malignant diseases, the goal of this therapy is 2-fold: host immunosuppression and tumor eradication. In the absence of an underlying tumor burden, conditioning chemotherapy in patients with NMD serves as a mechanism for host immune suppression or myelosuppression to promote engraftment of donor stem cells.

Broadly, there are 3 major categories of conditioning therapy, each defined by the intensity of marrow ablation and duration of cytopenia. They are classified as myeloablative conditioning that results in profound and prolonged, often fatal, pancytopenia in the absence of stem cell rescue; nonmyeloablative (NMA) conditioning that transitions to the donor without appreciable cytopenia; and reduced intensity conditioning (RIC) that has a brief period of myelosuppression and early recovery. (2) Myeloablative conditioning relies on pretransplant chemotherapy and/or radiation therapy at maximum tolerated doses. NMA relies on immune modulation and RIC uses a combination of both. Immune modulation is beneficial in both engraftment and GVHD prevention and is achieved with either serotherapy (antithymocyte globulin, alemtuzumab) or cell manipulation (T cell or selective T subset depletion).

Myeloablative conditioning can result in early and late organ toxicities, as well as increased transplant-related mortality, especially in the infant, but it also has the benefit of supporting engraftment better. RIC and NMA can be less toxic as a result of decreased intensity but may be associated with a higher risk of graft rejection. (2) RIC and NMA may also result in the simultaneous presence of donor and recipient cells after transplantation (mixed chimerism), which may be acceptable if there is adequate control of the underlying disease manifestations. (2) Thus, the choice

of conditioning regimen needs to be tailored according to disease requirement and donor source, and at no time does “one size fit all.”

Given a high risk of growth, neurodevelopment, endocrine and organ toxicities, as well as long-term risk of therapy-related malignancies, radiation therapy-based conditioning has been largely abandoned in infant HSCT for NMD. Although not completely safe, chemotherapy-based conditioning is preferred in infants over radiation. The most common among these are busulfan-based conditioning regimens, with more recent regimens using additional combinations of fludarabine, melphalan, and treosulfan. However, given their underlying organ immaturity, infants remain at increased risk for late effects of therapy. (3) In a recent study of 102 infants and young children who underwent busulfan-based myeloablative HSCT, 98% experienced at least 1 late effect of therapy, with nearly 65% experiencing 3 or more such effects. (3) Dental abnormalities were the most commonly observed late effect; endocrine, neurologic, pulmonary, visual, and immune manifestations were also observed.

## GVHD PROPHYLAXIS

Early inflammatory manifestations affecting the skin, gut, and liver are classified as acute GVHD whereas the fibrotic autoimmune late disorder that affects multiple organs is classified as chronic GVHD. The basis of GVHD prevention is either inhibition or depletion of T cells from the graft followed by slow recovery to establish graft versus host tolerance. GVHD prophylaxis is most commonly achieved with calcineurin inhibitors such as cyclosporine or tacrolimus, or the mammalian target of rapamycin inhibitor sirolimus in combination with mycophenolate mofetil, low-dose methotrexate, or corticosteroids. More recently, in mismatched or alternative donor transplants, posttransplantation cyclophosphamide on days 3 and 4 after stem cell infusion has been shown to effectively deplete activated alloreactive T cells, efficiently inhibiting GVHD, especially the chronic variety. Serotherapy (alemtuzumab, antilymphocyte globulin) used as part of conditioning therapy can also be protective against GVHD, depending on the timing of administration. Successful HSCT requires a balance of the benefits of donor T cells as they support engraftment and depletion of these cells to prevent GVHD.

## IMMUNE RECONSTITUTION

The process of immune conversion from recipient to donor leaves a period of immune deficiency when patients are

susceptible to life-threatening infections. Typically this period extends into the first few months after transplantation. Recovery is better after the initial 6 months when immune suppression used for GVHD prophylaxis is tapered and cellular recovery from the graft occurs. The presence of GVHD, however, results in intensification of immune suppression and can delay immune reconstitution. The acquired immune deficiency after transplantation is managed with close surveillance, emergent intervention, and infection prophylaxis against bacteria, fungi, viruses, and opportunistic infections.

Immunosuppressive conditioning regimens and lymphocyte depleted or naïve lymphocyte sources (umbilical cord blood) have a higher risk of infectious complications and delayed immune reconstitution. Typically, natural killer (NK) cells and CD8 T cells recover first, followed by B cells. CD4 T cells recover last and may take over a year to return to normal levels. Immunizations are withheld until immune recovery (for 6–12 months) and killed vaccines precede the use of live vaccines after the withdrawal of immune suppression. Compared with marrow transplants, cord blood and T-cell-depleted transplants have delayed immune reconstitution and hence a higher rate of late infections even in the absence of GVHD.

## TRANSPLANTATION APPROACHES BASED ON DISEASE

Indications and the ideal timing for HSCT in infancy vary and are based on disease manifestations. Early irreversible manifestations often necessitate HSCT early in infancy to prevent sequelae. The following discussion visits the most common nonmalignant diagnoses encountered in infancy that can be mitigated or modified with early HSCT. Disorders that may be recognized during infancy but typically await age and disease progression, such as sickle cell disease and adrenoleukodystrophy, are beyond the scope of this review.

### Inherited Bone Marrow Failure Syndromes

Inherited bone marrow failure syndromes are a group of rare disorders characterized by ineffective hematopoiesis, congenital anomalies, and predisposition to myeloid malignancy. The following is a summary of 2 of the more commonly encountered bone marrow failure syndromes that are seen in early infancy, and for which bone marrow transplantation provides curative therapy. Because of the predisposition to malignant transformation (leukemia) in these conditions, it is best to target full donor chimerism in congenital marrow failure syndromes, thus routing the clones with a predisposition to malignant transformation.

**Severe Congenital Neutropenia.** Severe congenital neutropenia (SCN) is an inherited bone marrow failure syndrome caused by an arrest in myeloid development at the promyelocyte stage. It is characterized by an absolute neutrophil count (ANC) of less than  $500/\mu\text{L}$  and predisposition to severe bacterial sepsis and malignancy (commonly myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML], though other leukemia subtypes can occur). Granulocyte colony-stimulating factor (G-CSF) is standard therapy for patients with SCN and decreases sepsis-related mortality from an estimated 6% to 7% per year to approximately 1% per year. (4) Responsiveness to G-CSF therapy is highly variable, often requiring very high doses. In addition, this therapy does not mitigate risk of transformation to MDS or AML. Although all patients with SCN are at risk for MDS or AML, a direct association exists between G-CSF responsiveness and subsequent risk of malignancy. In data obtained from the Severe Congenital Neutropenia International Registry, patients with decreased responsiveness to G-CSF were at significantly greater risk for AML or MDS. (4)(5) This “high-risk” group (defined by a persistently low median ANC of  $<2,188/\mu\text{L}$  [ $<2.2 \times 10^9/\text{L}$ ] despite the use of  $>8 \mu\text{g/kg}$  per day of G-CSF) was found to have a cumulative incidence of AML or MDS of 40% at 10 years. This is in contrast to more responsive patients (defined as those who required less than  $8 \mu\text{g/kg}$  per day of G-CSF to maintain an ANC of  $>2,188/\mu\text{L}$  [ $>2.2 \times 10^9/\text{L}$ ]) in whom the cumulative incidence of MDS or AML at 10 years was 11%. The risk of sepsis-related death is also greater in the high-risk population.

These data allow for consideration of HSCT in all patients with SCN, though failure to respond to G-CSF and malignant transformations are absolute indications for HSCT because of the high mortality from sepsis or refractory disease. Thus, transplantation should be strongly considered in high-risk patients who require large doses of G-CSF or those with known high-risk mutations. (5)(6) For other patients, transplantation is often still considered, though predominantly in the setting of an available HLA-matched sibling donor. Both myeloablative and RIC regimens have been used in SCN with similar survival. (7) Significantly better outcomes are observed in patients who are younger than 10 years. (8)

Malignant transformation results in poorer results and cure rates after HSCT. In a study by Fioredda et al, no significant difference in overall or event-free survival was observed between those patients who underwent HSCT with MDS/AML and those without (8); however, this finding is inconsistent with findings from previous studies, and may be a reflection of variability in disease status at the time of transplantation, improvement in pretransplantation therapy,

transplantation methods, and supportive care in the modern era. (9)(10)

**Congenital Amegakaryocytic Thrombocytopenia.** Congenital amegakaryocytic thrombocytopenia (CAMT) is an inherited bone marrow failure syndrome that results from a defect in the thrombopoietin growth factor receptor. It is characterized by decreased or absent megakaryocytes in the bone marrow and typically manifests with severe isolated thrombocytopenia at or soon after birth, generally with evidence of cutaneous bleeding (petechiae, purpura) or intracranial hemorrhage. Unlike other bone marrow failure syndromes, congenital anomalies are not observed in CAMT but evolution to MDS or leukemia can occur.

The clinical course remains variable in this condition. Patients with CAMT I (with complete loss of function of the thrombopoietin receptor) manifest evidence of severe persistent thrombocytopenia with rapidly progressive bone marrow failure. Patients with CAMT II (with some residual thrombopoietin receptor activity) demonstrate a more protracted course. (11)(12) The latter can have a transient increase in platelet count during the first year of life but ultimately progress to severe bone marrow failure by a median age of 48 months. (13) Platelet transfusions are administered for supportive care; antifibrinolytic therapy such as aminocaproic acid and/or tranexamic acid is used for symptomatic management of superficial bleeding.

HSCT is the only curative therapy available for CAMT, and the treatment of choice is HSCT from a matched sibling donor. In the absence of a suitable donor, alternative donor transplants are indicated, albeit with inferior overall survival and higher transplant-related mortality. (11)(14) RIC regimens are a recent development and have been reported in a small number of cases. (15) Myeloablative preparative regimens are historically more commonly used. Although transplantation timing needs to balance the toxic effects of transplantation at a very young age, the risk of bleeding manifestations, progressive aplasia, and potential evolution to acute leukemia are reasons for considering early HSCT with the best available donor. (14)(16)

### Inherited Metabolic Disorders

**Infantile Malignant Osteopetrosis.** Infantile malignant osteopetrosis (IMO) is an autosomal recessive disease caused by a defect in osteoclast activity that results in impaired bone resorption. It is characterized by multiple abnormalities including early-onset bone marrow failure, secondary immunodeficiency (because of ineffective medullary hematopoiesis), skeletal anomalies (macrocephaly, facial anomalies, and fractures), nasal obstruction, cranial nerve compression and dysfunction with visual abnormalities

and hearing loss, dental abnormalities, hepatosplenomegaly, short stature, hypocalcemia, and gross motor delay. (17)(18)(19) If untreated, IMO is fatal with a mortality rate of 70% by 6 years of age. (18)

Allogeneic stem cell transplantation is the only curative therapy for this condition and works by replacement with donor-derived osteoclasts. Recent data published by the Center for International Blood and Marrow Transplant Registry demonstrated improved overall survival with the use of an HLA-matched sibling donor for HSCT. (18) An alternative donor source should still be considered if an available sibling donor is not available. Although myeloablative conditioning regimens are commonly used in patients with IMO, emerging data suggest a potential role for RIC regimens in patients who are receiving a bone marrow or peripheral blood stem cell product. (20)

Graft failure is not uncommon in this condition and contributes substantially to posttransplantation mortality. (18) Other common posttransplantation complications include hepatic veno-occlusive and interstitial pneumonitis. Most children do not have progressive visual deterioration after transplantation; however, persistent visual impairment is not uncommon. (18)(21) Outcome data published by Orchard et al on 193 patients who underwent HSCT for IMO demonstrated complete resolution of hepatosplenomegaly in all surviving patients; likewise, normalization of calcium levels was also observed in all patients 1 to 2 years after transplantation. (18) Hearing loss is potentially though not definitely reversible. Many characteristic skeletal abnormalities resolve and can be monitored with serial radiography. (22) Based on long-term data from the European Group for Blood and Marrow Transplantation, no significant change in height velocity is typically observed after transplantation. (21)

It should be noted that not all forms of osteopetrosis are amenable to transplantation. For example, patients with *RANKL* mutations have end-organ resistance rather than osteoclast abnormality and cannot be cured with transplantation. Infants with *OSTM1* mutations have rapid progressive neurologic deterioration despite receiving a transplant at 3 months of age, and may either be refractory or require HSCT very early in life or in utero.

**Hurler Syndrome.** Hurler syndrome (or mucopolysaccharidosis type 1H) is a highly fatal autosomal recessive disorder that results from a deficiency in the lysosomal enzyme  $\alpha$ -L-iduronidase. Patients with this condition appear normal at birth but manifest early multisystem disease manifestations, including cardiopulmonary complications, visual disturbances with corneal clouding, hearing loss, skeletal anomalies, and progressive neurologic



deterioration. (23) Intravenous enzyme replacement therapy is available for use in this condition and should be initiated in all patients as adjunct therapy at the time of diagnosis (24); its use, however, does not prevent neurologic deterioration because of an inability to cross the blood-brain barrier. Comparatively, allogeneic stem cell transplantation can alter clinical and neurocognitive outcomes and is the current standard of care. (25)

HSCT provides a method for enzyme replacement to all organ systems, including the central nervous system. In a recent study published by Aldenhoven et al, normal  $\alpha$ -L-iduronidase enzyme levels after transplantation were associated with improved clinical outcomes, including cardiac, pulmonary, orthopedic, visual, and auditory outcomes. (26) Given this finding, only non-carrier-matched sibling donors should be used as donors to ensure high enzyme levels at engraftment. For patients in whom a matched sibling donor is not readily available, a suitable umbilical cord blood product should be considered if available. Utilization of cord blood products can shorten the interval to transplantation because medical clearance for live donation is circumvented. The use of cord products has demonstrated high rates of full donor chimerism and early normalization of enzyme levels. (27)(28)(29)

Unlike many other clinical outcomes, posttransplantation  $\alpha$ -L-iduronidase enzyme levels are not always predictive of neurocognitive outcomes. (26) Age at transplantation, however, remains highly predictive of neurocognitive outcomes. (26)(30) In a study of 31 patients with Hurler syndrome who underwent umbilical cord blood transplantation at various ages (categorized as 2–8 months old, 9–17 months old, and  $\geq 18$  months old), lower age at transplantation was shown to be associated with improved cognitive function, expressive and receptive language, and adaptive behavior. (30) The current recommendation is to perform transplantation in patients with Hurler syndrome before 8 months of age for best neurocognitive outcomes.

Busulfan-based myeloablative conditioning regimens are most commonly used to avoid graft rejection, though RIC regimens have also reported success. (28) Early referral for HSCT, however, remains the key to successfully treating patients with this disorder.

**Infantile Krabbe Disease.** Infantile Krabbe disease is a rare autosomal recessive neurodegenerative disease that results from a deficiency in the lysosomal enzyme galactocerebrosidase (GALC). (31) Deficiency in this enzyme results in accumulation of toxic metabolites with consequent central and peripheral demyelination. (32) Infants with this condition are generally well-appearing at birth but develop symptoms shortly thereafter, typically with

onset of disease manifestations within the first 6 months of age. Classic manifestations include irritability, feeding difficulties, blindness, deafness, seizures, cognitive impairment, progressive spasticity, and if left untreated, early childhood death. (33) Through engraftment of donor-derived enzyme (GALC)-producing cells, allogeneic HSCT functions as a potential treatment modality for patients with this condition; however, the efficacy of transplantation remains highly contingent on timing.

In 2005, Escolar et al showed that allogeneic HSCT improves neurodevelopmental and survival outcomes in infants with Krabbe disease when completed before the onset of symptoms. (33) Similar outcomes were not observed among infants who received transplants after the onset of symptoms. In a more recent study evaluating long-term outcomes in infants with early infantile Krabbe disease who received transplants at or before 2 months of age, Allewelt et al further demonstrated that improved functional outcomes can be achieved in infants who undergo allogeneic HSCT before 30 days of age. (32) Given these and previous findings, timely screening (newborn screen, family history) and emergent referral to a specialized tertiary care center remain critical in providing optimal care for these patients.

Given the urgency of transplantation and potential constraints in timely donor availability for patients with infantile Krabbe disease, umbilical cord blood is very commonly used as a donor source in this condition.

### Immunodeficiency Disorders: Severe Combined Immunodeficiency Disorder

Severe combined immunodeficiency disorder (SCID) is a primary immunodeficiency disorder caused by abnormal T-cell function and development. Multiple molecular defects have been linked to SCID and are associated with variable immunologic phenotypes, which are typically distinguished by the presence or absence of B cells and NK cells. The most common form of SCID, X-linked SCID, results from a mutation in *IL2RG* and has an immunologic phenotype characterized by low or absent T cells, low or absent NK cells, and present but dysfunctional B cells (T– B+ NK– SCID). (34)(35) Based on the defining molecular defect, other immunologic phenotypes (T– B+ NK+ SCID, T– B– NK+ SCID, and T– B– NK– SCID) can also be observed.

Historically, patients with SCID presented in early infancy with severe and recurrent opportunistic infections. With successful implementation of near-universal newborn screening, many patients can now be identified at birth and before the onset of infectious complications. Gene therapy is available for a subset of identified patients, including



patients with *ILGR2* gene mutation and with adenosine deaminase deficiency (35); clinical trials remain ongoing at this time. Access to gene therapy (a form of autologous transplantation) and long-term follow-up for disease eradication after introducing gene-modified cells remain current constraints to this therapeutic modality, which offsets the need for allogeneic HSCT.

Hence, for most patients, allogeneic stem cell transplantation remains the standard of care. With detection at birth, our current practice is to admit patients into isolation immediately after diagnosis to avoid exposure to pretransplant infections, and proceed to HSCT as soon as possible. Matched related donors are the preferred donor source in patients with SCID and have been associated with the highest overall survival. (36) Nonetheless, for patients without an available matched related donor, very good clinical outcomes have been demonstrated with the use of an alternative donor transplant, particularly in those patients who undergo transplantation before age 3.5 months and in those who do not have evidence of active infection at the time of transplantation. (37)(38)

Lack of functional T cells decreases the risk of graft failure, and many children with a complete SCID phenotype can successfully undergo transplantation without use of pretransplant conditioning. A retrospective analysis published by the Primary Immunodeficiency Treatment Consortium in 2014 demonstrated a 5-year overall survival rate of 97% in children who received a matched sibling donor transplant, most of whom did not receive pretransplant conditioning. (38) The need for a preparative regimen in patients undergoing HSCT for SCID depends on donor source, disease phenotype, pretransplant comorbidities, and a tendency for poor B-cell reconstitution following isolated stem cell infusion. Recent data support the use of some conditioning before HSCT to enhance donor-derived T-cell recovery and B-cell function. Clinical trials remain ongoing in this realm. (38)

### Immune Dysregulation Disorders

**Familial Hemophagocytic Lymphohistiocytosis.** Familial (or primary) hemophagocytic lymphohistiocytosis (fHLH) is a potentially fatal autosomal recessive immune dysregulation disorder that results from dysfunction in T- and NK-cell cytotoxicity, as mediated by gene defects in *PRF1*, *UNC13D*, *STX11*, *STXBP2*, or in some cases, as yet undefined gene mutations. (39) Clinical manifestations are highly variable but may include fever, hepatitis, coagulopathy, bone marrow failure (with anemia and thrombocytopenia), rash, pulmonary manifestations, and/or neurologic dysfunction. (40) Given the absence of an identifiable gene mutation in

some cases, the diagnosis of fHLH may be confirmed with either molecular diagnosis or the presence of specific clinical and laboratory features. (41) Chemotherapy and immunotherapy (typically etoposide, dexamethasone, and cyclosporine with or without intrathecal methotrexate) are important components of frontline therapy to suppress the dysregulated immune system; HSCT is required for cure and is best performed after symptom control. (42)

Similar outcomes have been demonstrated with the use of a matched related donor or matched unrelated donor in allogeneic HSCT for patients with hemophagocytic lymphohistiocytosis. (42) Given the heredity of fHLH and potential variability in age at presentation, all potential related donors should undergo disease screening (guided either by molecular diagnostics or surrogate laboratory and immunologic studies) as part of the donor screening evaluation.

Historically, a busulfan-based myeloablative conditioning regimen was used as standard of care in this condition. (39) Recent data, however, have demonstrated a significant survival advantage with the RIC regimens in children undergoing allogeneic stem cell transplantation for fHLH. (43)

**Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome.** Immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome is a rare primary immunodeficiency disorder that arises from hemizygous mutations in *forkhead box P3* (*FOXP3*)—a transcription factor that is highly expressed by regulatory T lymphocytes and is essential for maintaining self-tolerance. (44) Mutations in this transcription factor are associated with loss of function of regulatory T lymphocytes and result in life-threatening autoimmunity targeting the gut and other organs. Onset of symptoms typically occurs within the first month to year of age, most commonly with early-onset intractable diarrhea, skin rash, and type 1 diabetes. (45) Though less common, other systemic autoimmune manifestations may be observed, including but not limited to nephropathy, hepatitis, thyroid dysfunction (hyper or hypothyroidism), hepatitis, autoimmune cytopenia, and arthritis.

Current upfront therapy includes supportive care (nutritional support, hormone therapy, blood product transfusion, intravenous immunoglobulin) and single or multiagent immunosuppressive therapy. However, HSCT is the only curative therapy. In a recently published multicenter international retrospective study of 96 patients with IPEX syndrome, similar overall survival was observed in patients who received chronic immunosuppressive therapy and those

who underwent HSCT (86.8% vs 73.2%,  $P=.055$ ). Notably, persistent or new-onset autoimmune symptoms (not including GVHD) were significantly lower among patients who underwent transplantation versus those who received immunosuppressive therapy (17% vs 51%,  $P=.001$ ). (45)

Based on data from the aforementioned study, donor type, conditioning type, and age at transplantation do not significantly affect survival. (45) However, the extent of organ impairment before transplantation remains an important consideration. In their study, Barzaghi et al used a numerical scoring system to assess the extent of organ involvement before initiation of immunosuppressive therapy or transplantation. (45) Individual scores for each patient were determined based on the presence or absence of each of the following: malnutrition, intractable diarrhea, kidney dysfunction, liver dysfunction, or respiratory impairment (with 1 point given for each). Using this method, researchers demonstrated that transplant recipients with

more severe organ involvement (defined as a pretransplant score of  $\geq 3$ ) had poorer overall survival after HSCT. (45)

## SUMMARY

As described before, multiple disorders of infancy rely on HSCT for a cure. Transplantation methods and supportive care details continue to improve with new approaches and medications that support engraftment, reduce toxicity, and minimize GVHD. Transplantation outcomes have consistently improved over the past few decades because of rigorous clinical trials, most of which are from multicenter efforts, because of the rarity of the disorders in question. The Table provides a summary of recent outcome data of HSCT for different conditions. From the neonatologist's perspective, most of the disorders described require immediate referral to a tertiary care transplant center that is experienced in the care of the very young during transplantation. Immediate intervention is often key to

TABLE. Summary of Recent Outcome Data of HSCT for Different Conditions

INDICATION	AGE AT TRANSPLANT	DONOR	CONDITIONING	OUTCOMES / CONCLUSIONS
Krabbe syndrome (32)	N=19 Age at transplant: 19–61 days	Cord blood, marrow	Myeloablative	Survival 79%, better outcomes if HSCT <30 days of age
Hurler disease (26)	N=217 Age at HSCT: 2–47 months	Cord, marrow or peripheral blood	Majority myeloablative	Neurodevelopmentally significantly impaired if IQ <85 at transplant Best outcomes when HSCT at a young age (<8 months) and intact IQ Cord blood has higher enzyme levels (desirable)
HLH and related disorders (46)	N=46 14 infants	Bone marrow	Reduced intensity	Overall survival 67% at 18 months Graft rejection amenable to second transplant
Congenital bone marrow failure syndromes (non-Fanconi) (47)(48)	64 patients Age at HSCT: 2–12 years	Cord	Myeloablative	Survival after related cord HSCT: 95% Survival after unrelated cord HSCT: 61%
	11 patients Age at HSCT: 2–168 months	Cord or marrow	Reduced intensity	Survival: 82%
SCID (38)	68 patients Age at HSCT: <3.5 months	Marrow, peripheral blood or cord	None or reduced intensity or myeloablative	Survival if <3.5 months old: 94%
	172 patients Age at HSCT: >3.5 months			Survival if older or infected: 50%–82%
Infantile osteopetrosis (18)	N=193 Age at HSCT: <6–60 months	Cord or marrow	Myeloablative or reduced intensity	Survival 39%–62%; preferred before onset of disease sequelae

HLH=hemophagocytic lymphohistiocytosis, HSCT=hematopoietic stem cell transplant, SCID=severe combined immunodeficiency disorder.

preservation of function and even survival. The future holds great promise for even better transplantation approaches and expanding donor pools, as well as gene-modified autologous transplants for amenable disorders.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical features and differential diagnosis of neonates with immune deficiencies.
- Know the initial screening tests and subsequent specific diagnostic tests used to evaluate neonates with possible defects in host defense mechanisms.

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## Hematopoietic Stem Cell Transplantation: A Neonatal Perspective

Erin Hall and Shalini Shenoy

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# Index of Suspicion in the Nursery

## 1 Bilious Vomiting in a Term Neonate

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### PRESENTATION

A 2.34-kg male infant is born to a gravida 3 woman with 2 previous abortions at 37.1 weeks of gestation. A cesarean delivery is performed because of fetal distress with oligohydramnios and abnormal Doppler ultrasonography findings. The antenatal period is largely uneventful, with second-trimester antenatal anatomy ultrasound scan reported as normal. However, fetal growth is noted to be poor (lag of 2 weeks) on antenatal ultrasonography at 34 weeks and abnormal Doppler findings are reported at 37 weeks. The neonate does not require any active resuscitation at birth and is transferred to the NICU for low-birthweight care. Intravenous fluids are started initially in view of abnormal antenatal Doppler ultrasonography findings and feedings are introduced at around 21 hours after birth. First meconium is passed at 6 hours of age. The neonate, however, develops



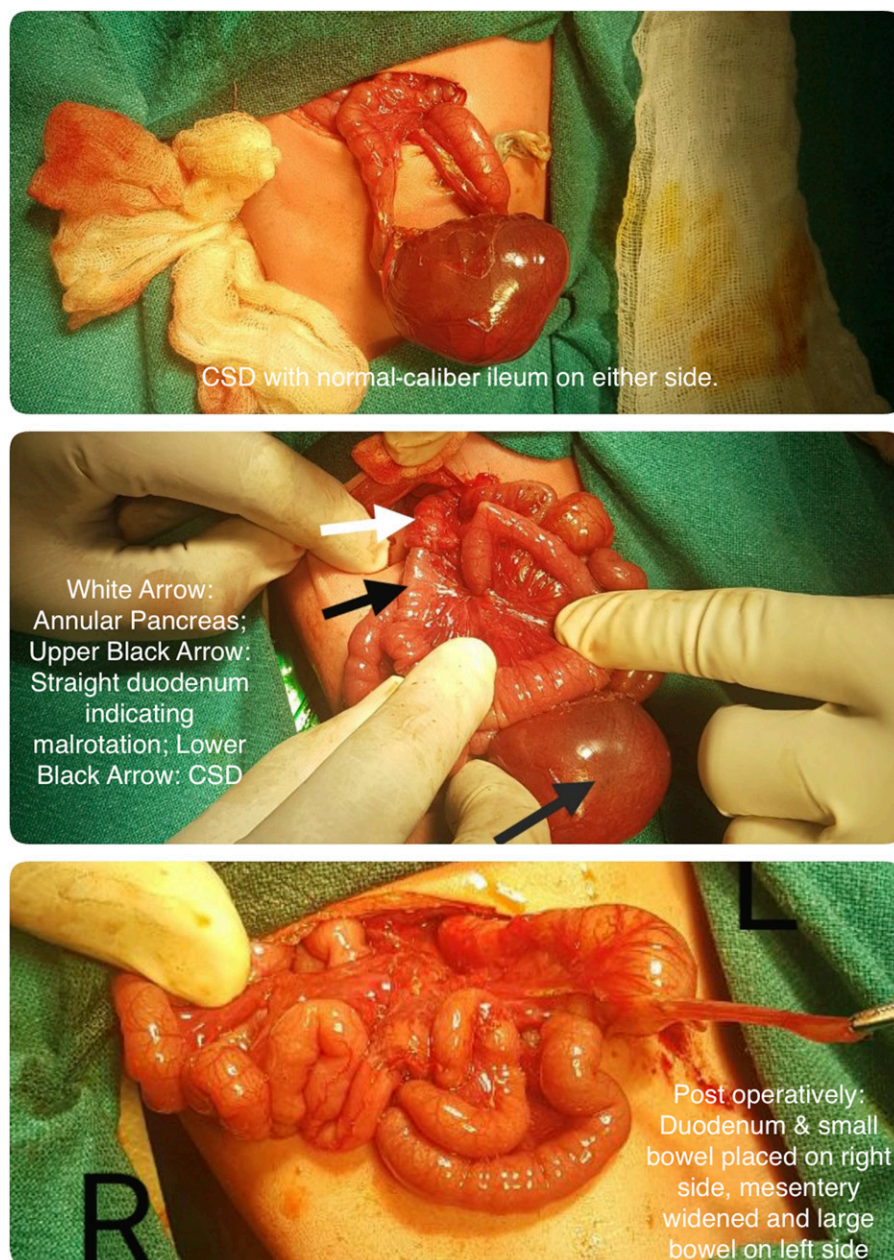
Figure 1. Supine radiograph suggesting the presence of a large cystic structure in the right iliac fossa.

**AUTHOR DISCLOSURE** Drs Goel, Mittal, and Arora have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

feeding intolerance in the form of bilious vomiting and abdominal distention on the second day. Sepsis screening result is negative (total white blood cell count:  $7,500/\mu\text{L}$  [ $7.5 \times 10^9/\text{L}$ ]; absolute neutrophil count:  $2,850/\mu\text{L}$  [ $2.85 \times 10^9/\text{L}$ ]; C-reactive protein:  $0.1 \text{ mg/dL}$  [ $9.5 \text{ nmol/L}$ ]; platelet count:  $230 \times 10^3/\mu\text{L}$  [ $230 \times 10^9/\text{L}$ ]; peripheral smear: no toxic granules).

In view of the bilious vomiting, volvulus, malrotation, and intestinal obstruction are included in the differential

diagnosis and abdominal radiography is ordered. Supine radiography (Fig 1) suggests the presence of a large cystic structure in the right iliac fossa, which persists on serial radiography. Pediatric surgery consultation is sought and a conservative approach is advised. The neonate is now kept nil per os (nothing by mouth) with the addition of a prokinetic agent (domperidone). Feedings are reintroduced after 24 hours (day 3 after birth) but it again leads to bilious vomiting; repeat radiography suggests persistence of the same cystic



**Figure 2.** Congenital segmental dilation (CSD) with normal-caliber ileum on either side. White arrow shows annular pancreas; upper black arrow, straight duodenum indicating malrotation; lower black arrow, CSD.

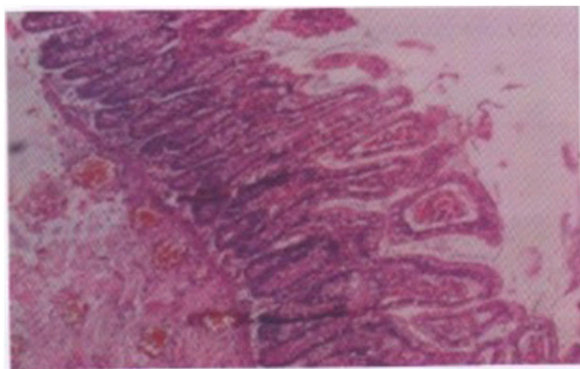
shadow in the right iliac fossa. Exploratory laparotomy is planned for the neonate on the 4th day after birth.

Laparotomy reveals cystic dilation of the ileum with malrotation, along with an incidental finding of an asymptomatic annular pancreas. The dilated ileal segment is 5×4 cm in size with continuation of normal ileum on either side of the dilated segment (Fig 2). Because the primary pathology is cystic dilation of ileum, which is causing intestinal obstruction, resection of the dilated bowel along with end-to-end ileal anastomosis is performed. Malrotation can cause problems later on, so the Ladd procedure is performed, which includes surgical division of the Ladd band and widening of small intestine mesentery (Fig 2). An appendectomy is also performed at the same time, followed by reorientation of the small bowel on the right side and caecum and colon on the left side. Annular pancreas is left intact because it is not found to be causing any duodenal obstruction. Histopathology (Fig 3) shows all layers of intestine with normal intestinal mucosa and without any heterotopic tissue, consistent with the diagnosis of congenital segmental dilation (CSD) of the ileum.

## DISCUSSION

### The Condition

Also known as “segmental dilation of the ileum,” CSD is a dilated full-thickness segment of the ileum with normal-caliber ileum on either side. It is a rare condition of unknown etiology with about half of the cases presenting in the neonatal period. (1) CSD is characterized by the Swenson and Rathauser criteria as: 1) limited bowel dilation with a 3- to 4-fold increase in caliber, 2) an abrupt transition between dilated and normal bowel, 3) no internal/external barrier distal to the dilation, 4) a clinical picture of intestinal obstruction (complete or partial) 5) a normal neuronal plexus, and 6) complete recovery after



**Figure 3.** Histopathologic findings in all layers of intestine with normal intestinal mucosa and without any heterotopic tissue.

resection of affected segment. (2) The cause of CSD remains unknown. Postulated mechanisms include surrounding structures such as vitelline vessels and omphaloenteric bands compressing on the bowel loops at both ends, leading to focal segmental dilation without altering the bowel histology. (3)

It can present as an isolated entity or can be associated with other congenital malformations as seen in the current case, where it was associated with malrotation. To our knowledge, this is the first case in the literature in which CSD coexisted with asymptomatic annular pancreas. The clinical presentation is generally nonspecific, with the affected neonate developing features of bowel obstruction in the form of abdominal distention and bilious vomiting. Differential diagnoses include malrotation, volvulus, and intestinal obstruction because of other causes. Constipation can sometimes be associated, in which case Hirschsprung disease also becomes a possibility in the differential diagnosis.

### Diagnosis

Antenatal ultrasonography can sometimes suggest a dilated bowel loop. Waters et al (4) and Paradiso et al (5) described the antenatal ultrasonographic features associated with CSD. In the current case though, antenatal ultrasonography findings were reported as normal. Postnatal diagnosis requires a high index of suspicion but the diagnosis is usually made only during exploratory laparotomy performed for clinical intestinal obstruction. Supine and erect radiography suggests a dilated loop of bowel in right iliac fossa (as seen in the current case) with or without air fluid levels but with an otherwise normal gas pattern in the rest of the bowel. (6) Rarely, barium enema studies are also ordered but usually reveal findings similar to those seen on plain radiography.

### Treatment and Prognosis

Definitive treatment is resection of the dilated segment, followed by end-to-end anastomosis of the pre- (proximal) and post- (distal) ends. Prognosis is usually excellent after surgical resection. In the current case also, the surgery was well tolerated and the infant remained stable in the postoperative period. He continued to receive parenteral nutrition support for the next 3 days, after which feedings were initiated and gradually increased as tolerated. Full feedings were reached on the 10th postoperative day. The infant was discharged from the hospital on day 18 after birth, breast-feeding and doing well on follow-up and gaining adequate weight.

### Lessons for the Clinician

- A high index of suspicion is required for considering a diagnosis of CSD in a neonate with features of intestinal obstruction.
- Radiography is suggestive but not diagnostic, which is usually confirmed during laparotomy performed for intestinal obstruction.
- Prognosis is usually excellent after surgical resection of the dilated segment and end-to-end anastomosis of the normal-caliber ileum.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the morphogenesis of the GI tract and factors that lead to congenital malformations.

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## Case 1: Bilious Vomiting in a Term Neonate

Nitin Goel, Manish Mittal and Rohit Arora

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# Index of Suspicion in the Nursery

## 2 Infant with Early Direct Hyperbilirubinemia

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### PRESENTATION

A female infant was born at 37 weeks, 1 day of gestation via cesarean delivery because of late decelerations. No resuscitation was needed, and Apgar scores of 8 and 9 were assigned. The mother reported receiving prenatal care, and her prenatal laboratory tests were positive for group B *Streptococcus* (GBS) carriage, and negative for gonococcus, hepatitis B, chlamydia, HIV, and rapid plasma reagin (RPR).

After the first round of breastfeeding, the neonate's abdominal girth increased from 33 to 35 cm, and she had visible jaundice without any rash. Laboratory results from an evaluation at 6 hours of age included the following:

- Complete blood cell count: White blood cells 12,500/ $\mu$ L ( $12.5 \times 10^9$ /L); neutrophils 55.1% (22% bands, 40% segmented neutrophils); platelet count  $170 \times 10^3$ /uL ( $170 \times 10^9$ /L); hemoglobin 16.5 g/dL (165 g/L), and hematocrit 50%
- Chemistry: Total bilirubin 5.5 mg/dL (94  $\mu$ mol/L); direct bilirubin 2.5 mg/dL (43  $\mu$ mol/L); aspartate aminotransferase (AST) 58 U/L (0.97  $\mu$ kat/L); alanine aminotransferase (ALT) 17 U/L (0.28  $\mu$ kat/L); alkaline phosphatase 356 U/L (5.9  $\mu$ kat/L)
- C-reactive protein: 2.14 mg/dL (204 nmol/L)

She started treatment with intravenous ampicillin and gentamicin for presumed GBS infection. At 16 hours after birth, the C-reactive protein had increased to 7.34 mg/dL (699 nmol/L), and the total and direct bilirubin increased to 7.4 mg/dL (127  $\mu$ mol/L) and 3.6 mg/dL (62  $\mu$ mol/L), respectively.

On arrival at the NICU, she was active and in no distress in room air, with subtle dysmorphic facies, clear breaths, and no heart murmur, and her abdomen was full but not tense, without hepatomegaly. Laboratory findings on admission included an ALT of 12 U/L (0.2  $\mu$ kat/L), AST of 57 U/L (0.95  $\mu$ kat/L), and direct bilirubin of 4.0 mg/dL (68  $\mu$ mol/L).

### DIFFERENTIAL DIAGNOSIS

- Biliary atresia
- Alagille syndrome
- Early-onset sepsis
- Hepatitis
- Congenital infections

### CASE PROGRESSION

Abdominal ultrasonography demonstrated a contracted gall bladder with multiple echogenic foci, which could represent gallstones, and a normal common bile duct.

**AUTHOR DISCLOSURES** Drs Kumbhat, Folkins, Hawksley, and Cohen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Hepatology consultation suggested that the conjugated hyperbilirubinemia was likely secondary to an extrahepatic biliary obstruction. Treatment with oral ursodiol was started at 10 mg/kg every 8 hours.

Genetics was consulted for her subtle dysmorphic features, which included a flattened nasal bridge, prominent creases under the eyes, and tented lip. Echocardiography and eye examination, conducted as a part of the genetic evaluation, showed normal findings. Chest radiography performed for placing a peripherally inserted central catheter showed a hemivertebra at T-6. Conjugated hyperbilirubinemia and hemivertebrae are 2 of the 5 clinical diagnostic criteria for Alagille syndrome. (1) *JAG1* and *NOTCH2* sequencing and deletion/duplication analysis were performed (Prevention Genetics, Marshfield, WI), results of which were negative.

An evaluation for infectious diseases included a lumbar puncture with normal cerebrospinal fluid (CSF) studies. Polymerase chain reaction for blood and CSF was negative for enterovirus and herpes virus DNA, and surface viral cultures were negative. Urine cytomegalovirus result was negative. Blood cultures were negative. On the 4th day after birth, the pathologist noted that the placenta and umbilical cord showed necrotizing phlebitis without chorioamnionitis, concerning for a congenital infection, specifically congenital syphilis.

The placenta weighed 611 g, which is in the 90th to 95th percentile for a gestational age of 37 weeks. Microscopic examination (Fig 1) demonstrated necrotizing umbilical vasculitis and funisitis. The inflammatory infiltrate in the umbilical cord was

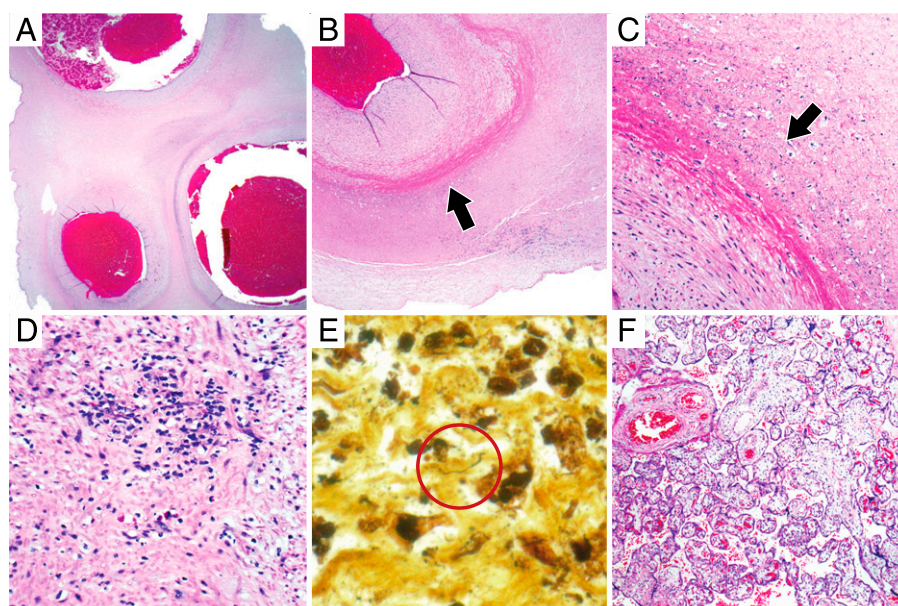
composed of mixed acute and chronic inflammatory cells, including plasma cells. The villi demonstrated patchy nonspecific villous edema but were otherwise unremarkable. No evidence was found to suggest an ascending chorioamnionitis. Both a Warthin-Starry stain and an immunohistochemical stain for spirochetes showed rare, small corkscrew-shaped spirochete organisms in the umbilical cord. The placental pathology was consistent with congenital syphilis.

Based on these findings, RPR titers and CSF VDRL tests were performed. The RPR test result was positive at 1:1,024, and CSF VDRL was positive at 1:8, consistent with congenital syphilis. Her skeletal survey showed fraying of multiple metastases with periosteal reaction along the long bones, consistent with congenital syphilis (Fig 2).

Ampicillin and gentamicin were discontinued, and the neonate was given a 10-day course of penicillin 50,000  $\mu$ /kg. Both parents retested positive for syphilis serology subsequently. Infectious disease, genetics, and gastroenterology followed up the infant after discharge. On her most recent gastroenterology follow-up, her  $\gamma$ -glutamyltransferase and direct bilirubin levels were normal, and ursodiol was discontinued.

## DISCUSSION

Hepatosplenomegaly is a common presentation for congenital syphilis, but isolated direct hyperbilirubinemia is not. Cholestasis often is a nonspecific response to any systemic stress, resulting in a self-limiting “idiopathic neonatal hepatitis.”



**Figure 1.** Microscopic pictures of the placenta. A. Low-power image of umbilical cord with rings of necrosis surrounding the umbilical vessels (H&E,  $\times 2$ ). B. Closer image of necrosis (black arrow) around the umbilical vessel (H&E,  $\times 4$ ). C. Necrotic debris (black arrow) in the Wharton jelly around the umbilical vessel (H&E,  $\times 20$ ). D. Predominantly chronic inflammatory cells in the Wharton jelly of the cord (H&E,  $\times 40$ ). E. Spirochete organism (black spiral in red circle) (Warthin-Starry,  $\times 60$ , image cropped to show organism). F. Chorionic villi with edema (H&E,  $\times 10$ ).

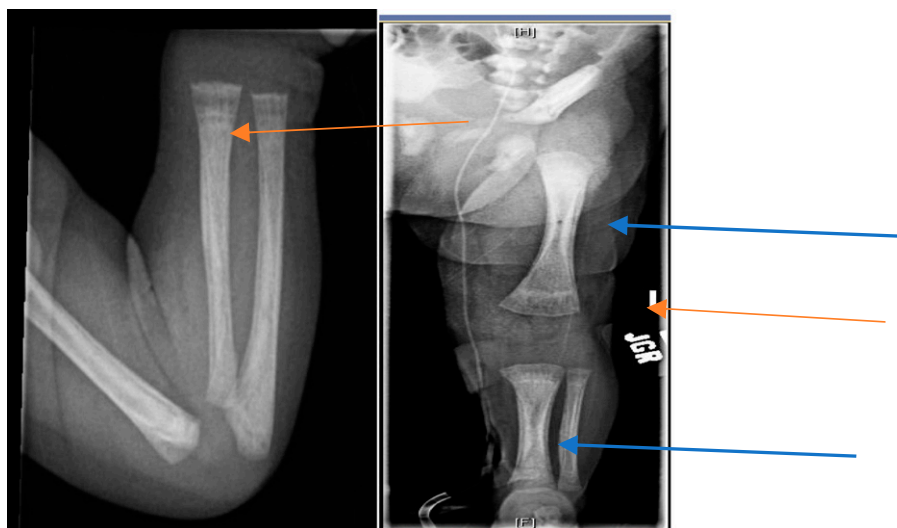


Figure 2. Metaphyseal changes (red arrows) and periosteal changes (blue arrows) in long bones.

However, it might be a presenting sign of serious infectious or metabolic disease (20%) or anomalies of the biliary tract (25%). (2) Most of the infectious causes of cholestasis are viral, which only represent 5% of the cases of neonatal cholestasis.

In the current case, the infant had isolated direct hyperbilirubinemia without any other symptoms of congenital syphilis. The maternal prenatal laboratory values were not significant for syphilis. This directed us down the path of noninfectious causes of direct hyperbilirubinemia, for which the results were negative.

The screening algorithms for congenital syphilis recommended by the Centers for Disease Control and Prevention (CDC) include screening with serologies. Maternal treponemal and nontreponemal immunoglobulin G antibodies are transmitted transplacentally, which complicated the interpretation of neonatal serologic test results. Congenital syphilis cannot be ruled out if a neonate has a nonreactive treponemal and nontreponemal test. (3) This makes the diagnosis of syphilis in neonates challenging. In the current case, the placental pathology was crucial in guiding this infant's evaluation.

Congenital syphilis continues to remain a problem in spite of an available cure. (4)(5) During 2015-2016, the CDC reported that the rate of syphilis in women rose by 35.7%. The rate of reported congenital syphilis rose by 86.9% from 2012 to 2016. (2) Given the resurgence of congenital syphilis worldwide, clinicians need to keep this diagnosis in mind when presented with isolated direct hyperbilirubinemia in a newborn, even if maternal serology was negative early in gestation.

#### Lessons for the Clinician

- Isolated initial direct hyperbilirubinemia is an uncommon presentation of congenital syphilis.

- Given the resurgence of congenital syphilis worldwide, clinicians need to keep it in mind when presented with isolated direct hyperbilirubinemia.
- Placental pathology was crucial in guiding the evaluation for this infant; special stains are needed to identify treponemes.
- Consider the diagnosis of congenital syphilis even with negative maternal serology, especially if not repeated in the second trimester or at delivery.

Note: This case is based on an oral presentation by Drs Kumbhat, Folkens, and Cohen at the Western Society for Pediatric Research conference; January 27, 2018; Carmel, CA.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations and diagnostic features of perinatal infections with *Treponema pallidum*.

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# Index of Suspicion in the Nursery

## 3 Hypermetabolic State in an Infant

Nitya Nair, MD,\* Ting Ting Fu, MD,\* Beth Haberman, MD\*

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### PRESENTATION

A 2,340-g male infant is born vaginally at 34 weeks of gestation to a mother with a history of asthma and hyperthyroidism. The pregnancy is overall uncomplicated except for preterm labor, and the delivery is notable for meconium-stained amniotic fluid and unknown group B *Streptococcus* status treated with 2 doses of penicillin. The infant does well initially with Apgar scores of 8 and 9, but soon develops tachycardia, tachypnea, and hypoxemia; radiography demonstrates respiratory distress syndrome with a small pneumothorax. Nasal cannula is needed to maintain normal oxygen saturations, and septic evaluation result is negative. Examination is notable for the vital signs described before, a barrel-shaped chest, and hyperreflexia. He is started on gavage feeds and treated with phototherapy for hyperbilirubinemia. On day 7 after birth, he suddenly develops worsening tachycardia to the 200s, tachypnea with respiratory distress, and decreased perfusion with mottling. Echocardiography reveals severe cardiac dysfunction, prompting transfer to the cardiac intensive care unit for stabilization. Laboratory results that day confirm the diagnosis.

### DISCUSSION

Differential diagnosis for this neonate with tachycardia, tachypnea, and hypoxemia initially includes infectious diseases such as sepsis or viral infection; pulmonary diseases such as pneumothorax, congenital pneumonia, or meconium aspiration syndrome; cardiovascular diseases such as structural heart disease or arrhythmia, inborn errors of metabolism, hypovolemia, or anemia; and endocrine diseases such as hyperthyroidism. The infant's diagnosis was confirmed to be neonatal Graves disease when laboratory tests showed thyrotropin less than 0.005 mIU/L (normal 0.4–4.0 mIU/L), free thyroxine 5.73 ng/dL (74 pmol/L; normal 0.9–2.5 ng/dL [12–32 pmol/L]), triiodothyronine 3.34 ng/mL (0.05 nmol/L; normal 1.2–3.0 ng/mL [0.02–0.05 nmol/L]), and thyroid-stimulating immunoglobulin 240% (normal <130%).

Neonatal Graves disease is caused by transplacental passage of maternal stimulatory thyrotropin receptor antibodies. It typically presents within the first week after birth and is self-limited up to 3 months until the maternal antibodies disappear from the infant's circulation. Although neonatal thyrotoxicosis is most commonly seen in the setting of active maternal Graves disease, it can also occur in the context of treated maternal Graves disease, as in this case. Presenting symptoms for neonatal Graves disease include tachycardia, hyperthermia, hypertension, irritability, feeding difficulties, poor weight gain, goiter, prematurity and low birthweight, microcephaly, hepatosplenomegaly, heart failure, cholestasis, and exophthalmos. (1)

**AUTHOR DISCLOSURES** Drs Nair, Fu, and Haberman have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



First-line therapy includes an antithyroid medication such as methimazole and a  $\beta$ -adrenergic blocker such as propranolol. Propylthiouracil is avoided because of an association with liver failure. (2) Potassium iodide is added in refractory cases, and glucocorticoids can be used in extremely ill neonates. (1) If left untreated, neonatal hyperthyroidism can have dangerous long-term sequelae, including a mortality rate up to 25%. (3)

## PATIENT COURSE

During his admission, the infant developed cachexia despite hyperphagia, conjugated hyperbilirubinemia (total bilirubin up to 28 mg/dL [479  $\mu$ mol/L] on day 12 after birth), and transaminitis (alanine aminotransferase up to 376 IU/L [6.3  $\mu$ kat/L] and aspartate aminotransferase up to 294 IU/L [4.9  $\mu$ kat/L]) on day 23 after birth. Potential infectious causes of conjugated hyperbilirubinemia were ruled out, and liver ultrasonography confirmed normal anatomy. Bilirubin levels declined as thyroid levels normalized. After extensive discussion among the primary, endocrine, and hepatology teams regarding the possibility of drug-induced liver injury, captopril was discontinued without any significant changes in transaminase levels. Methimazole was then halved and weaned, leading to a subsequent improvement in transaminase levels and normalization by age 2 months. Thyroid function results continued to normalize despite this medication adjustment. He has since been evaluated and treated for several issues including poor growth with advanced bone age, anaphylaxis, congenital hydrocephalus requiring ventriculoperitoneal shunt placement, and shunt-induced bicoronal craniosynostosis. He continues to work with multiple subspecialty teams to coordinate his care.

## Lessons for the Clinician

- Although neonatal thyrotoxicosis is most commonly seen in the setting of active maternal Graves disease, it

can also occur in the context of treated maternal Graves disease. (1)

- Presenting symptoms for neonatal Graves disease include tachycardia, hyperthermia, hypertension, irritability, feeding difficulties, poor weight gain, goiter, prematurity and low birthweight, microcephaly, hepatosplenomegaly, heart failure, cholestasis, and exophthalmos. (1)
- First-line therapy includes an antithyroid medication such as methimazole and a  $\beta$ -adrenergic blocker such as propranolol. (2)
- Methimazole is known to cause liver injury and subsequent cholestasis, so hepatic function tests must be monitored carefully and therapeutic effects of such medications must be weighed against their capacity to cause liver injury. (2)
- If left untreated, neonatal hyperthyroidism can have dangerous long-term sequelae, including a mortality rate up to 25%. (3)

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis.

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### Case 3: Hypermetabolic State in an Infant

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## Decreased Fetal Movement

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

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TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

#### Interpretation

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

- Bradycardia not accompanied by absent variability
- Tachycardia
- Minimal or marked baseline variability
- Absent variability without recurrent decelerations
- Absence of induced accelerations after fetal stimulation
- Recurrent variable decelerations with minimal or moderate variability
- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

- Absent variability with any of the following:

- Recurrent late decelerations
- Recurrent variable decelerations
- Bradycardia

- Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum FHR monitoring:

nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## CASE PRESENTATION

A 36-year-old gravida 1 para 0 pregnant woman comes to her obstetrics office at 33 weeks, 2 days of gestation with a perception of decreased fetal movement. The patient had been receiving routine prenatal care without complications. An office nonstress test was nonreactive and therefore, fetal ultrasonography was recommended. A biophysical profile was 6 of 8 (−2 for fetal breathing). Given the equivocal 6/10 testing in the setting of decreased fetal movement, the woman was sent to the labor and delivery department for further evaluation.

Her pregnancy was complicated by diet-controlled gestational diabetes and gestational hypertension. She was prescribed trazodone and bupropion for treatment of anxiety and depression.

## CASE PROGRESSION

On arrival at the labor and delivery department, her vital signs were normal. She denied any loss of fluid. On initial monitoring, the following FHR tracing was noted (Fig 1).

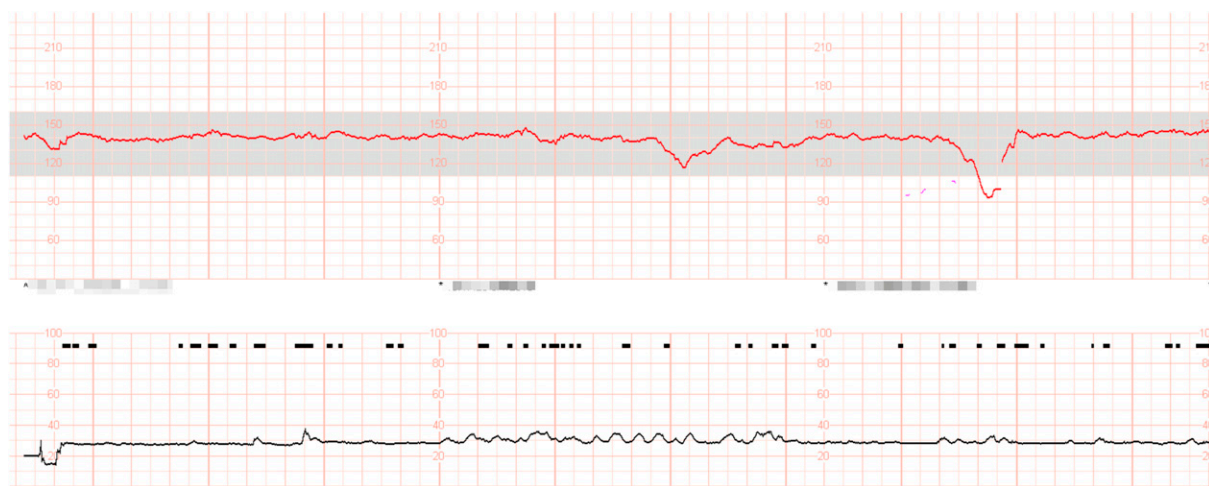


Figure 1. Electronic fetal monitoring strip 1.



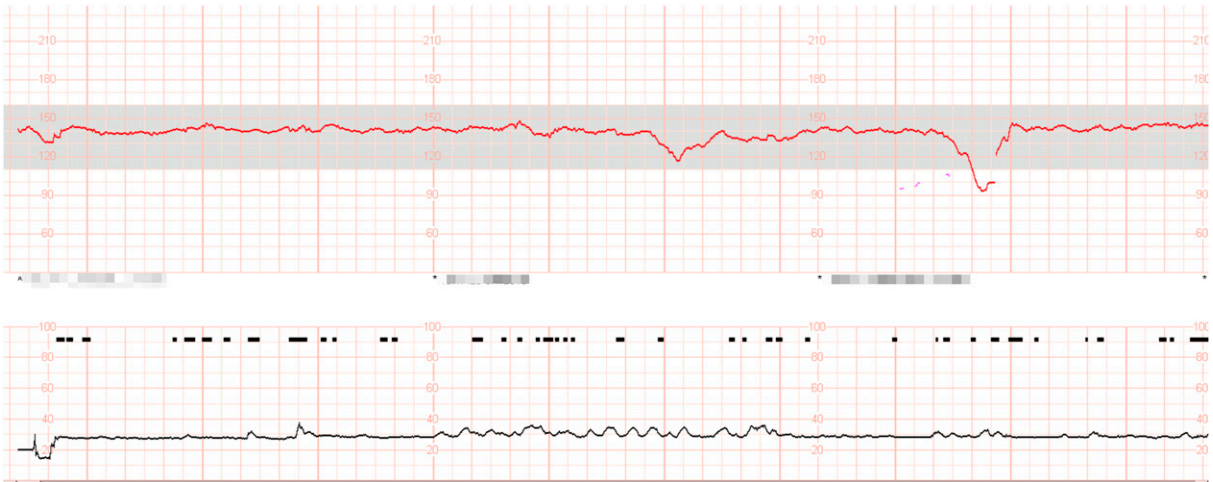


Figure 1. Electronic fetal monitoring strip 1.

Findings in Fig 1 are as follows:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: Intermittent variable decelerations to 90 to 100 beats/min
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Umbilical cord compression, idiopathic, uteroplacental insufficiency
- Action: Continuous monitoring, change maternal position, obtain biophysical profile

On examination, the woman appeared well and in no distress. Fetal ultrasonography demonstrated intrauterine growth restriction with an estimated fetal weight of 1,060 g (1st percentile) with oligohydramnios. Interrogation of the umbilical artery Doppler revealed absent end-diastolic flow. A repeat biophysical profile was 8/8. Maternal-fetal medicine was consulted for recommendations about further management. Betamethasone was recommended for fetal lung maturity given the possibility of a premature delivery. After ultrasonography, the following fetal tracing was noted (Fig 2).

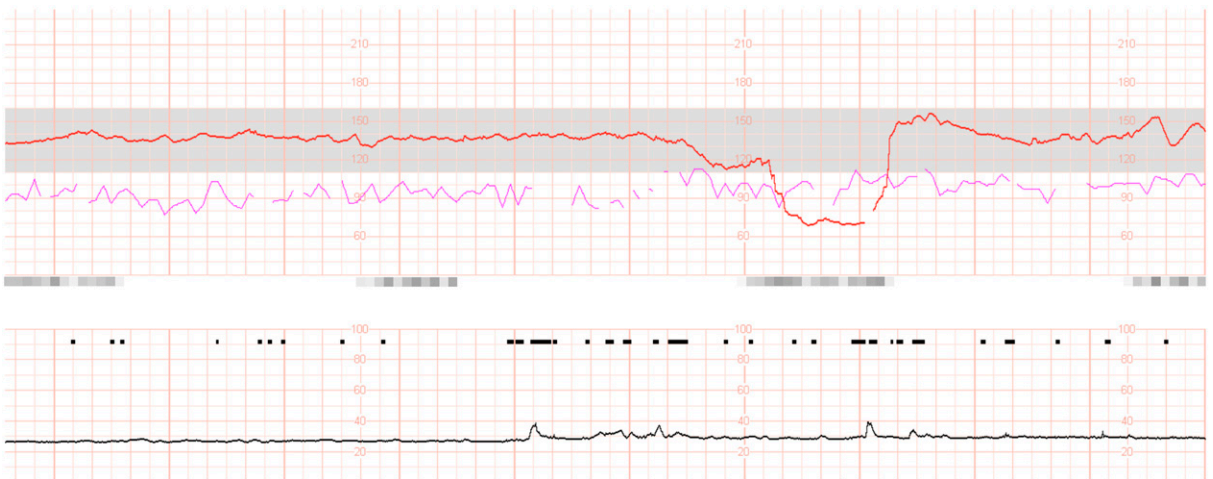


Figure 2. Electronic fetal monitoring strip 2.



Figure 2. Electronic fetal monitoring strip 2.

Findings in Fig 2 are as follows:

- Variability: Minimal to moderate
- Baseline rate: 135 beats/min
- Episodic patterns: Variable deceleration to nadir 70 beats/minute, lasting 2 minutes
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II tracing with variable deceleration and subsequent rebound tachycardia before return of baseline; moderate variability is present
- Differential diagnosis: Uteroplacental insufficiency, umbilical cord compression, idiopathic
- Action: Continuous fetal monitoring, change maternal position

Given this variable deceleration, ongoing fetal surveillance was advised. Assuming fetal testing was reassuring, the goal of care was to provide expectant management until at least 48 hours after the patient's initial dose of betamethasone. During continuous fetal monitoring, the following fetal tracing was noted (Fig 3).

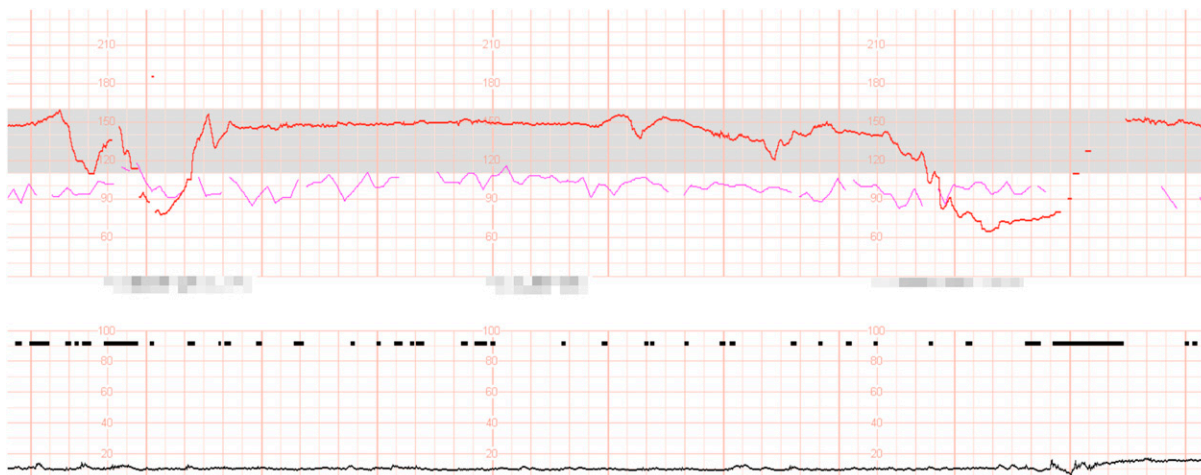


Figure 3. Electronic fetal monitoring strip 3.

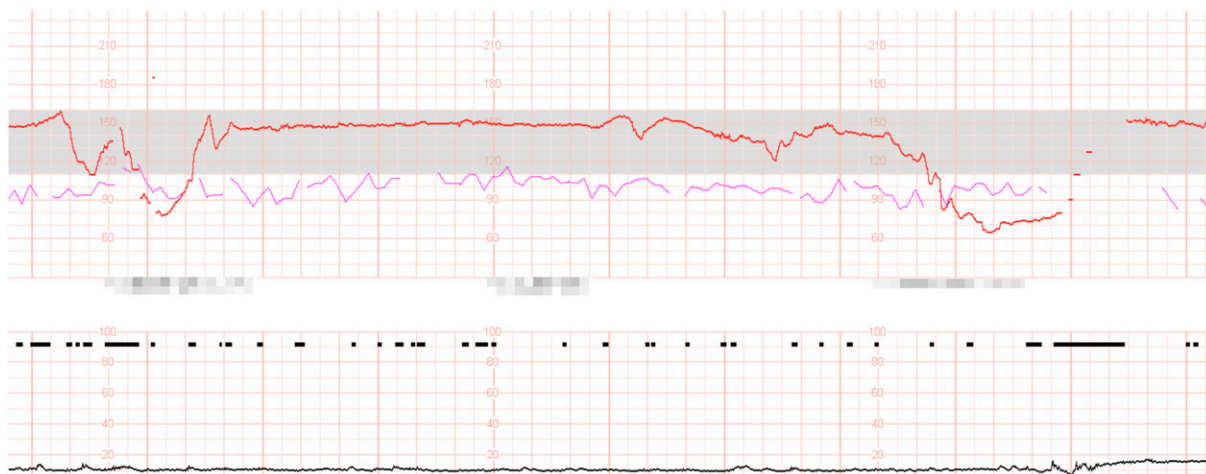


Figure 3. Electronic fetal monitoring strip 3.

Findings in Fig 3 are as follows:

- Variability: Minimal to moderate
- Baseline rate: 150 beats/min
- Episodic patterns: Variable decelerations to nadir 65 beats/min, lasting 2.5 minutes
- Periodic patterns: None
- Uterine contractions: None
- Interpretation: Category II tracing with variable deceleration and subsequent return to baseline, variables noted to become deeper and longer, though moderate variability noted afterwards
- Differential diagnosis: umbilical cord compression, decreased fetal oxygenation, placental insufficiency, idiopathic
- Action: Given category II tracing with more frequent and progressive variable decelerations in the setting of decreased fetal movement, and evidence of uteroplacental insufficiency based on ultrasound and fetal surveillance, delivery was recommended.

The patient was transported to the operating room and underwent urgent cesarean delivery. Intraoperative findings were notable for a narrow lower uterine segment. A classic uterine incision was made. After delivery, delayed cord clamping was performed for 30 seconds. The cord was clamped and cut, and the infant was handed to the awaiting NICU team.

## OUTCOME

A viable male infant was delivered at a gestational age of 33 weeks, 2 days via urgent primary classic cesarean delivery; his birthweight was 1,120 g (1st percentile) and Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. Because the Apgar scores were satisfactory, cord gases were not obtained. The infant

emerged active and vigorous and was brought to the radiant warmer where he was dried and stimulated. His initial examination was notable for significant growth restriction. His head circumference measured 27.5 cm (2nd percentile) with a length of 37 cm. The infant was transferred to the NICU for further care. He was on room air and did not require respiratory support nor did he have any evidence of hemodynamic instability. The infant was initially hypoglycemic but responded well to intravenous fluids with dextrose and tolerated gastric feedings. The infant was tolerating full gastric feedings 7 days after birth. He had feeding immaturity and apnea of prematurity. He was discharged from the hospital after an 8-week stay in the NICU. The infant is currently doing well at home.

The placental pathology demonstrated a singleton placenta weighing 148 g (<10th percentile for gestational age). There was an unremarkable 3-vessel cord with fetal membranes with hemosiderin-laden macrophages, suggestive of chronic abruption. The small placental body had an infarction involving 20% of the disc including scattered central microinfarcts and larger peripheral infarcts.

## DISCUSSION

Decreased fetal movement is a common reason that pregnant women seek obstetric evaluation. Obstetric providers routinely advise active fetal movement monitoring for their patients. Perceived active fetal movement is one means of evaluating fetal well-being. Decreased fetal movement is reported by at least 40% of women in one large study (1); most of the time decreased fetal movement episodes are short-lived and result in reassuring obstetric outcomes.

Persistent decreased fetal movement can be associated with fetal compromise. Maternal perception of decreased

fetal movement may identify the fetus that is experiencing uteroplacental compromise and possibly provide an opportunity to intervene before the onset of metabolic acidosis and ultimately stillbirth. Although studies demonstrate an association between decreased fetal movement and adverse outcome, a systemic review of randomized controlled trials did not support a clear benefit of increasing women's awareness of the need for prompt evaluation in the setting of decreased fetal movement. (2) The test characteristics of decreased fetal movement are difficult to study given multiple confounders and lack of standardization of an individual's perception.

Perception of fetal movement is one of a number of modalities for evaluating fetal status. Additional means of evaluating fetal status include a nonstress test, prolonged fetal monitoring, oxytocin contraction stress test, biophysical profile ultrasonography, and umbilical artery Doppler velocimetry. (3)

A woman who reports decreased fetal movement may be instructed to perform kick counts or undergo further fetal evaluation with one of the described modalities before. The differential diagnosis of perceived decreased fetal activity includes fetal sleep states, maternal medications that cross the placenta (such as trazodone as prescribed for this patient), maternal smoking, uteroplacental insufficiency, maternal acid-base disturbances, fetal-maternal hemorrhage, infection, neuromuscular disease, and severe fetal anemia.

Evaluation should include an assessment of both the maternal and fetal compartments in a prompt fashion. Commonly, maternal vital signs, a focused maternal physical examination, and a fetal nonstress test or biophysical profile are performed. The goal of the evaluation is to determine whether there are any indicators of fetal compromise such as uteroplacental insufficiency from fetal growth restriction, as was determined in the current case.

On evaluation, this patient underwent fetal testing that required further prolonged evaluation because fetal acidemia could not be excluded. During expectant management, the fetal decelerations progressed in frequency and severity concerning for impending fetal compromise. The decelerations did not resolve despite intrauterine resuscitation with

maternal repositioning and rehydration. In the setting of the ultrasound findings suggestive of uteroplacental insufficiency, the fetal decelerations were likely the result of depressed blood flow from increased placental resistance. Despite prematurity and less than 48 hours from her initial course of betamethasone, delivery was the appropriate step in management. A reassuring outcome was obtained for both the mother and neonate.

In a future pregnancy, this patient will be at risk for recurrent fetal growth restriction from uteroplacental insufficiency.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the indications for and fetal/newborn complications of cesarean delivery.
- Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow measurements, in assessment of fetal conditions and well-being.
- Understand the rationale, interpretation, and limitations of maternal detection of fetal movement, of the biophysical profile, the nonstress test, and the contraction stress test as means of assessing fetal well-being.
- Know how to evaluate fetal growth rate and fetal growth restriction and the management of fetal growth restriction.
- Know the significance of oligohydramnios and the management of pregnancy when it is diagnosed.

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## Strip of the Month: Decreased Fetal Movement

Laura Smith and Brett C. Young

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**Strip of the Month: Decreased Fetal Movement**

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## Scalp Swelling and Spinal Dimpling in Two Term Infants

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### CASE 1

A female neonate is noted to have a painless scalp swelling on routine newborn examination.

#### Prenatal and Birth Histories

- Born to a 36-year-old, gravida 1, para 2-0-0-2 woman
- Prenatal course complicated by dichorionic-diamniotic twin pregnancy
- Estimated gestational age: 37 weeks
- Scheduled cesarean section for breech presentation, delivery without vacuum or instrumentation of head
- Prenatal laboratory values unremarkable
- Apgar scores: 7 and 8 at 1 and 5 minutes, respectively

#### Presentation

Routine newborn examination on the 1st day after birth was notable for a focal 1.2-cm swelling adjacent to the sagittal suture midway between the anterior and posterior fontanelles (Fig 1).

### PROGRESSION

#### Vital Signs

- Blood pressure: 64/43 mm Hg
- Pulse: 116 beats/min
- Temperature: 36.8°C (98.2°F)
- Respiratory rate: 40 breaths/min
- Oxygen saturation: 100% (in room air)

#### Physical Examination (Day 1)

- Birthweight: 2.81 kg (17th percentile), length: 50 cm (74th percentile), head circumference 32 cm (5th percentile)
- General: Alert and in no distress
- Head: Normocephalic, atraumatic, anterior fontanelle open, soft, flat. A focal 1.2-cm cystic swelling immediately adjacent to the sagittal suture midway between the anterior and posterior fontanelles was found during routine palpation of the cranial suture lines. The swelling felt cystic and was fluctuant, but did not extinguish with pressure. The adjacent parietal bones were overlapping along the suture with the bone plate contralateral to the swelling being the more superior of the 2 bone plates. No defect was palpated in the bone plates. The overlying skin was normal without thinning, color change, tenderness, or pitting. Hair distribution was normal.

**AUTHOR DISCLOSURE** Drs Schuh and Berkowski have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Cystic scalp lesion anterior to the posterior fontanelle.

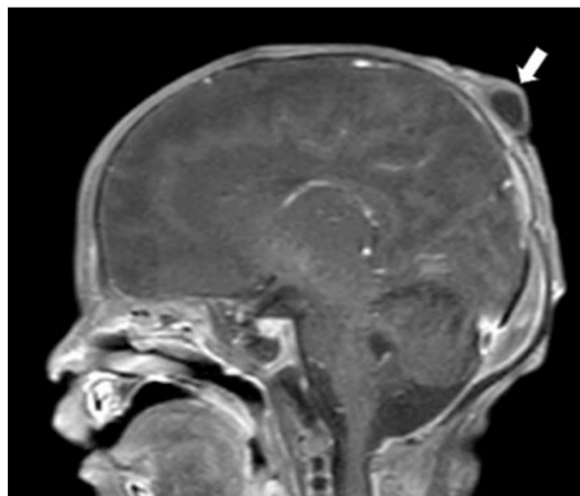


Figure 2. Cystic scalp lesion visualized on sagittal T1-weighted magnetic resonance imaging scan.

- Eyes: Pupils equal, round, reactive to light, red reflex present bilaterally
- Mouth: Intact palate
- Neck: Supple without lymphadenopathy or thyromegaly
- Lungs: Clear to auscultation bilaterally
- Heart: Regular rate and rhythm, normal S<sub>1</sub>, S<sub>2</sub>, no murmur
- Abdomen: Soft, nontender, nondistended, no masses, no hepatosplenomegaly, normoactive bowel sounds
- Genitourinary: Normal female, patent anus
- Back: Spine straight and sacrum normal
- Neurologic: All extremities move spontaneously, good tone, and normal reflexes

### Radiographic Studies

Ultrasonography and subsequent magnetic resonance imaging (MRI) revealed a 10 × 11 × 9 mm, well-defined, cystic lesion with a fluid level centered in the subcutaneous tissues of the right paramidline scalp near the posterior fontanel (Fig 2) with an associated thin fluid communication to the intracranial compartment (Fig 3).

## CASE 2

A newborn male presents with a spinal dimple.

### Prenatal and Birth Histories

- Born to a 32-year-old, gravida 3, para 2-0-1-2 woman
- Prenatal course uncomplicated
- Estimated gestational age: 36 weeks
- Urgent cesarean section for preterm labor in the setting of placenta previa

- Prenatal laboratory findings unremarkable
- Apgar scores: 8 and 9 at 1 and 5 minutes, respectively

### Presentation

Routine newborn examination on the 1st day after birth was remarkable for a dimple with a 0.3-cm-wide base over the lumbar spine (Fig 4).

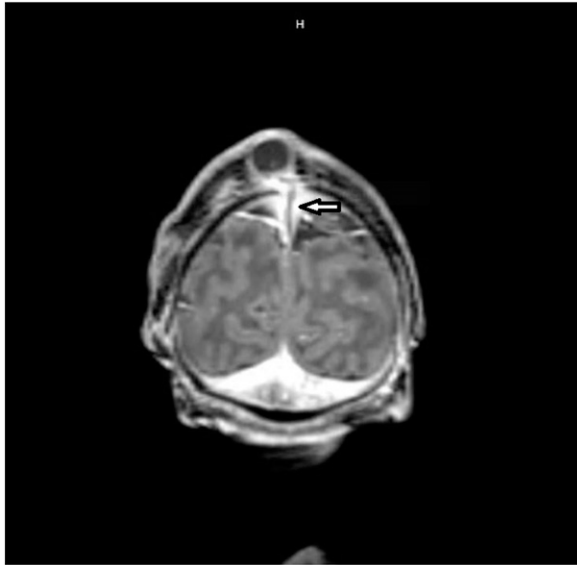
## PROGRESSION

### Vital Signs

- Pulse: 128 beats/min
- Temperature: 37.4°C (99.3°F)
- Respiratory rate: 50 breaths/min
- Oxygen saturation 99% (in room air)

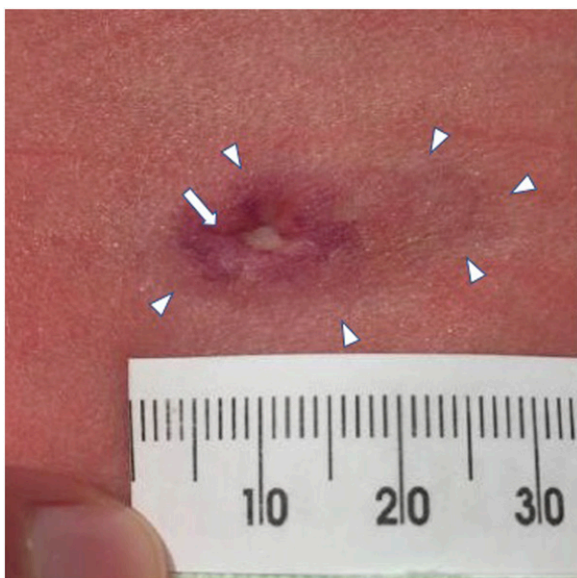
### Physical Examination (Day 1)

- Birthweight: 3.4 kg (37th percentile), length: 51.4 cm (68th percentile), head circumference: 34.3 cm (21st percentile)
- General: Alert and no distress
- Head: Normocephalic, atraumatic, anterior fontanelle open, flat and soft
- Eyes: Pupils equal and reactive, red reflex present bilaterally
- Mouth: Intact palate
- Neck: Supple with no lymphadenopathy or thyromegaly
- Lungs: Clear to auscultation bilaterally
- Heart: Regular rate and rhythm, S<sub>1</sub>, S<sub>2</sub> normal; a 1/6 systolic murmur was best heard at left sternal border
- Abdomen: Soft, nontender, nondistended, no hepatosplenomegaly



**Figure 3.** Communication between cystic scalp lesion and intracranial compartment visualized on coronal gadolinium-enhanced T1-weighted magnetic resonance imaging scan.

- Genitourinary: Normal male with bilaterally descended testes, patent anus
- Back: Lumbar dimple approximately 1-mm deep with the base fully intact and visible, centered in an irregularly shaped 3×1-cm purple patch that was surrounded by a thin ring of hypopigmentation. Palpation of the underlying spine did not reveal a gross abnormality.
- Neurologic: All extremities move spontaneously, good tone, and normal reflexes. The infant voided and passed stools normally.



**Figure 4.** Lumbar dimple with arrow indicating discoloration around dimple, and arrowheads highlighting area of hypopigmentation.

## Radiographic Studies

Ultrasonography and subsequent MRI revealed a thickened band of neural tissue extending from the dorsal aspect of the conus medullaris and communicating with a dermal sinus tract extending to the cutaneous lesion at approximately the L3 level (Fig 5).

## DIFFERENTIAL DIAGNOSIS

Two infants presented separately with a painless cystic scalp lesion and a lumbar dimple, and neither seemed to be adversely affected, with intact neurologic function.

The differential diagnosis for these lesions in a newborn depends on the location and may include:

- Atretic meningocele
- Caput succedaneum
- Dermoid cyst
- Dermoid sinus tract
- Encephalocele
- Lipoma
- Occult spinal dysraphism
- Sebaceous cyst
- Sinus pericranii
- Traumatic cyst
- Tumor
- Vascular malformations

## ACTUAL DIAGNOSIS

Both infants were diagnosed with an atretic meningocele.

The infant in case 1 was evaluated by pediatric neurosurgery soon after birth, with outpatient follow-up. The infant remained asymptomatic at her 1- and 6-month appointments. Neurosurgery plans to proceed with surgical removal at 1 year of age for cosmetic reasons and to prevent risk of future injury/infection.

The infant in case 2 underwent a tethered cord release that was performed at 5½ months of age. Pathology confirmed an atretic lipomeningocele.

## WHAT THE EXPERTS SAY

Cranial atretic meningoceles are a form of arrested neural tube defect in which the meninges are extruding through the skull. When cranially located, they fit into a broader category of lesions known as cephaloceles, which are small, subdermal lesions that usually extend through the skull and may contain central nervous system tissue.



**Figure 5.** Lumbar lesion with cord tethering visualized on sagittal T1-weighted magnetic resonance imaging scan. Arrow indicates site of fatty attachment of the lesion to conus medullaris at L1, and arrowhead highlights site and tract of dimple at L3.

(1)(2) Cephaloceles are often midline, particularly if atretic, and are divided into 2 groups, encephaloceles and meningoceles. (2)(3) Encephaloceles contain meninges and neuroglial tissue, such as the brain, while meningoceles only contain the meninges. (1)

Less commonly, atretic meningoceles can be found over the spine, where they are a type of closed spinal dysraphism. (4) In spinal cases, a fibrous band, often with atretic nerve routes, connects to spinal tissue and may terminate cutaneously. The literature is controversial regarding whether or not they truly contain meninges, calling into question whether the lesion is truly an interrupted meningocele. (5)

Patients with a cephalic atretic meningocele will typically present with a subcutaneous midline cyst or mass on an apparently intact skull, which is often diagnosed with ultrasonography. (2)(6) These masses are sometimes associated with intracranial pathology. Further imaging findings that support a

diagnosis of atretic cephalocele are abnormalities of the superior sagittal sinus, persistence of the prosencephalic vein of Markowski, and other midline cerebral abnormalities. (7)

Spinal atretic meningoceles were previously described as a small, flat, or depressed area of dysplastic skin that may be surrounded by hyperpigmentation or a salmon-colored capillary malformation that looks like a “cigarette burn.” (4)

Both cephalic and spinal atretic meningoceles can be, but are not always, painful to touch. (4)(8) They are at risk for growing or ulcerating over time. (3)(8) Although some are detected in infancy, they are often not seen on prenatal ultrasonography and subsequently missed at birth; some have escaped detection until the teenage years or even adulthood. (9)(10)

Cephalic and spinal atretic meningoceles are widely thought to be caused by a defect in secondary neurulation, or possibly a defect in caudal neural tube regression following secondary neurulation in the case of spinal atretic meningoceles. (4)(5)(7)

Ultrasonography is widely accessible and can help exclude more serious possibilities on the differential diagnosis for an atretic meningocele. When available at your institution, we suggest obtaining a brain/spine MRI in the immediate newborn period because it can often be done without sedation during the first few days after birth, thereby minimizing risk to the patient. Treatment of an atretic meningocele depends on the size, symptoms, and associated risks. Atretic meningoceles that are painful, enlarging, ulcerating, or at risk for injury or for causing neurologic deficits need to be addressed surgically.

Symptoms and comorbidity dictate prognosis, particularly if there are associated brain or spine anomalies. (7) The atretic meningocele itself is often benign and outcomes after surgical resection are usually good. (6)

Although the clinical picture for both of these infants may have fit multiple diagnoses on the differential, the most important key to diagnosis was further imaging. Neither infant had a history of delivery trauma, making caput succedaneum or traumatic cyst less likely, and the size of the cyst was smaller than expected for a caput.

Note: These cases were presented by Drs Schuh and Berkowski as part of the workshop, The Not-so-Well “Well” Newborn: Clinical Conundrums in the Nursery at Pediatric Hospital Medicine 2018 in Atlanta, Georgia. The workshop was led by Dr Lindsey Skibley.

## ACKNOWLEDGMENTS

The authors wish to thank J. Andrew Berkowski, MD, and Jocelyn Schiller, MD, for their review of this article.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical and imaging findings, treatment, and outcomes of abnormalities of neuronal proliferation, migration, and myelination (eg, holoprosencephaly, agenesis of the corpus callosum, lissencephaly, and schizencephaly).
- Know the embryology, prevention, incidence, and differential diagnosis of myelomeningocele and encephalocele.
- Know the clinical and imaging findings, treatment, and outcome of myelomeningocele and encephalocele.
- Recognize the clinical features and know how to diagnose craniofacial anomalies.
- Know how to recognize and differentiate complications of soft tissue injury to an infant's scalp, like caput and subgaleal bleed.
- Know the clinical features, diagnosis, management and outcome of neurocutaneous disorders including neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, etc.

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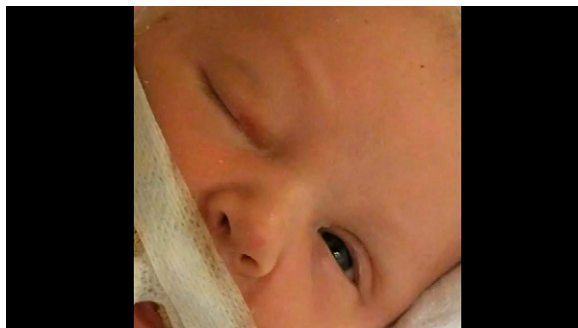


## An Infant with Abnormal Eye Movements

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**Video 1.** Click here to view the video. Reproduced with permission of Akshaya Vachharajani, MD, copyright 2018.

Please view Fig 1 and watch the accompanying video clip (Video 1).

The most likely cause of this infant's examination findings is:

(Note: More than 1 option is possible.)

- A. Left Horner syndrome.
- B. Left cranial nerve II (optic nerve) palsy.
- C. Right cranial nerve III (oculomotor nerve) palsy.
- D. Right cranial nerve IV (trochlear nerve) palsy.
- E. Right cranial nerve VI (abducens nerve) palsy.

The video clip depicts an intubated term female infant with abnormal right eye findings. The infant's left eye is normal: the eye opens completely and the left pupil reacts normally to light (video time 0:06 seconds). Her left eyeball is moving downward in the midline (video time 0:21 seconds), medial, and lateral (video times 0:23 and 0:25 seconds, respectively) positions. In contrast, her right eye does not open (video time 0:02 seconds), is immobile, and she has a right gaze preference with the right eyeball fixed downward and outward. This gaze preference persists even when the left eye is moving laterally (video time 0:23 seconds). The infant has bilateral forehead wrinkling (video time 0:27 seconds). Her nasolabial creases on both sides are normal. Her tongue moves appropriately and sometimes protrudes (video time 0:24 seconds). She is able to move her neck throughout the clip.

The accompanying photograph (Fig 1) shows the infant's dilated right pupil that is fixed (ie, the pupil remains dilated even with bright light). As shown in Video 1, the infant's right eye does not open spontaneously, and hence the eyelids had to be opened manually. The right eyeball is noted to be in the downward and outward location.

The ophthalmologic findings in this infant are consistent with a right cranial nerve III palsy (right ptosis, dilated fixed pupil).

**AUTHOR DISCLOSURE** Drs Herco, Soloveychik, and Vachharajani have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Accompanying photograph of infant in video clip.

Pupillary constriction in response to light, also known as the light reflex, results from stimulation of the efferent parasympathetic fibers that are located in the part of the Edinger-Westphal nucleus of cranial nerve III. As the efferent fibers return to the eye, they are located in the superficial portion of the third cranial nerve. As a result of their

superficial location, these are the first fibers to be injured if there is external compression of cranial nerve III from any intracranial etiology. Thus, a fixed dilated pupil is an early sign of injury to cranial nerve III.

The levator palpebrae superioris muscle supplies the upper eyelid and is composed of 2 types of muscles. The striated part of the muscle is the major component and is supplied by cranial nerve III. The ptosis in this infant is caused by paralysis of the levator palpebrae superioris, and hence, is consistent with a third nerve palsy. The smooth muscle component of the levator palpebrae superioris is a small part of the entire muscle and is supplied by the sympathetic fibers. Injury to the sympathetic trunk causes Horner syndrome and partial ptosis, which has not occurred in this infant.

The infant's fixed downward and outward gaze is caused by the unopposed actions of the fourth (trochlear nerve) and sixth (abducens) cranial nerves. These nerves, respectively, supply the superior oblique muscle, which rotates the eyeball downward and outward and the lateral rectus muscle, which moves the eyeball laterally. All the other

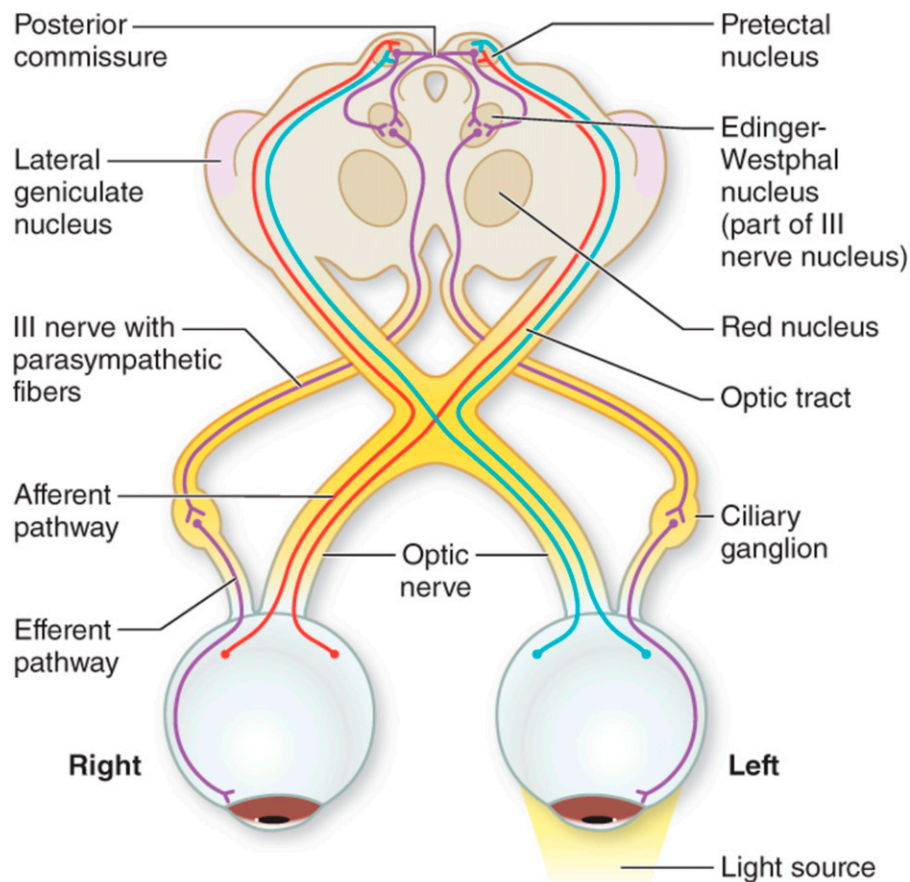
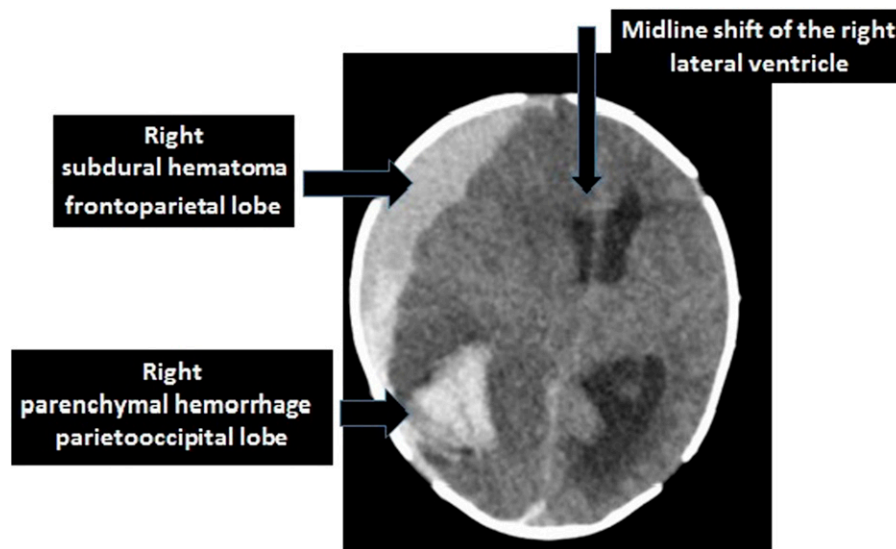


Figure 2. The anatomy of cranial nerve III. Printed with permission from Ropper AH, Samuels MA, Klein JP, eds. Disorders of ocular movement and pupillary function. In: *Adams & Victor's Principles of Neurology*. 10th ed. New York, NY: McGraw-Hill; 2014; chap 14.



**Figure 3.** Labeled image from the infant's computed tomography scan of the brain showing a right subdural hematoma with midline shift of the right lateral ventricle.

extraocular muscles (the medial, superior, and inferior recti, and the inferior oblique) are supplied by cranial nerve III and hence are paralyzed.

The oculomotor nerve originates from the anterior part of the midbrain. It travels through the cavernous sinus and enters the orbit through the superior orbital fissure. At the fissure, it divides into a superior and inferior part. The superior branch motor innervation includes the superior rectus and the voluntary (striated) part of the levator palpebrae superioris (with the involuntary portion of the muscle being controlled by sympathetic fibers). The inferior branch carries motor innervation to the inferior rectus, medial rectus, and superior rectus muscles. The superior branch also carries sympathetic fibers to the superior tarsal muscle and the inferior branch carries parasympathetic fibers to the ciliary ganglion to innervate sphincter pupillae and ciliary muscles. Because cranial nerve III travels through the cavernous sinus, it is affected in patients with a cavernous sinus thrombosis. In patients with increased intracranial pressure, the nerve can be compressed by herniation of the uncus gyrus of the temporal lobe as it passes through the tentorial opening, causing the clinical findings of cranial nerve III palsy. The anatomy of cranial nerve III is shown in Fig 2.

The infant's other cranial nerves appear intact, including the following:

- Normal bilateral cranial nerves VII (ie, facial nerve): Normal wrinkling of the forehead and nasolabial creases

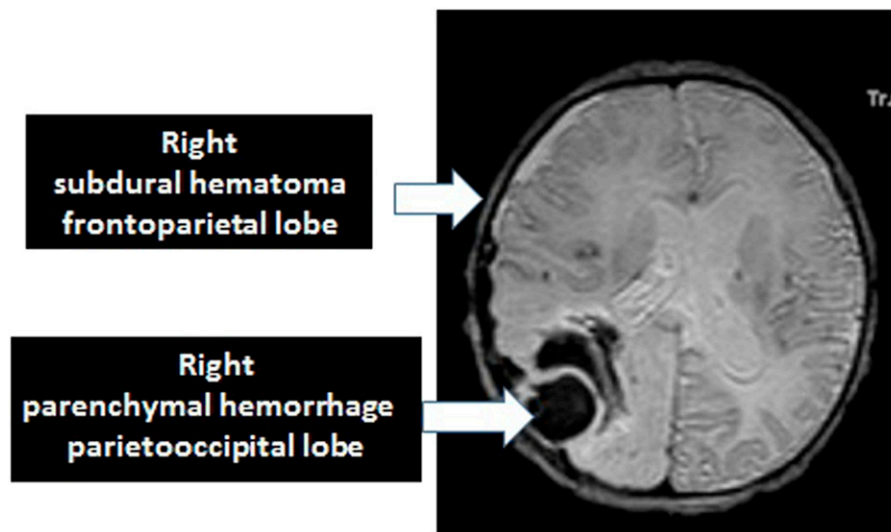
- Normal bilateral cranial nerves XI (ie, accessory nerves): Normal neck movements because of normal sternocleidomastoid and muscles
- Normal bilateral cranial nerves XII (ie, hypoglossal nerve): Normal tongue movements because of normal tongue muscles supplied by the nerve

The infant depicted in the video clip was born at term via vaginal delivery in a vertex presentation. The delivery was uncomplicated. The infant's birthweight was 3,470 g (58th percentile), head circumference was 35.5 cm (72th percentile), and length was 50.3 cm (47th percentile). She received the standard dose of vitamin K at birth. The infant breastfed well initially, but with subsequent feeding was noted to be more lethargic with a decreased heart rate, hypothermia, and apnea. She was transferred to a level 3 NICU, where she was given oxygen for continued apnea.

The neonatologist noted the infant's fixed dilated pupil and requested an emergent magnetic resonance imaging (MRI) of the brain, which revealed a right subdural hematoma, midline shift, and concern for brainstem herniation. The images from the level 3 NICU were not available for review.

The infant was transported to the tertiary NICU and underwent computed tomography (CT) scanning of the brain (Fig 3) and additional MRI of the brain (Fig 4).

The neurosurgery team was consulted and treated the right subdural hematoma by needle aspiration in the operating room. Head ultrasonography showed improvement in midline shift, but the patient's physical findings did not improve as she continued to be comatose with fixed/dilated pupils. An additional CT scan was obtained, which showed



**Figure 4.** Labeled image from the infant's brain magnetic resonance imaging scan showing a right subdural hematoma.

continued midline shift with significant blood remaining. She returned to the operating room, where 2 burr-holes were placed, which allowed additional bloody fluid to drain. She was then transferred back to the NICU. The infant had electroencephalographic seizures that were treated with phenobarbital and a midazolam infusion, and subsequently with levetiracetam. These electrical seizures stopped 24 hours after commencing antiseizure medications. Initially, she was not breathing spontaneously, which was attributed to the combination of raised intracranial pressure, presumed brainstem injury (a new finding of an absent gag reflex was found), and the antiseizure medications.

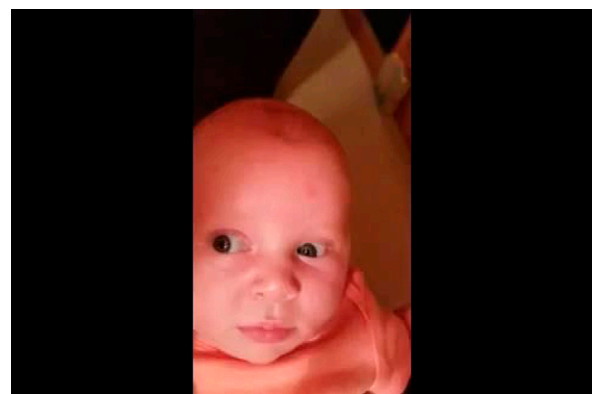
After several days, she began moving all 4 extremities and withdrawing to light touch. Her gag reflex slowly returned before spontaneous respirations were noted. Her invasive mechanical ventilatory support was slowly weaned, and after her spontaneous respirations became consistent, she underwent successful extubation to room air. She was initially fed through nasogastric tube gavage, but was able to feed orally after extubation. She was discharged at 12 days of age with her physical examination revealing right ptosis and mydriasis with minimal pupillary reactivity in the right pupil. The remainder of her physical examination findings were unremarkable, with normal appendicular tone, spontaneous movement of all 4 extremities, and no clonus. A video of her clinical examination findings at 35 days of age is shown in Video 2.

Although no definite cause of her subdural and intraparenchymal hemorrhage has been identified, multiple concerning underlying disorders have been effectively ruled out. These include coagulopathy, subdural venous thrombosis, and arteriovenous malformation. Nonaccidental trauma is

also less likely because no retinal hemorrhages were noted on further ophthalmologic examination.

Correct answer: C. Right cranial nerve III (oculomotor nerve) palsy.

The other options are incorrect. Horner syndrome (option A), characterized by partial ptosis, miosis, enophthalmos, heterochromia iridis, and anhydrosis on the ipsilateral side, is not seen in this infant. This infant has normal left eye findings with a normal pupillary response to light and lack of ptosis. The optic nerve is an afferent nerve and transmits sensory impulses to the midbrain and has no motor component and does not innervate any extraocular muscle. Injury to the optic nerve would cause light reflex to be absent on the side of the injury but would not cause ptosis. Hence option B is incorrect. The infant's right trochlear (cranial nerve IV) and abducens nerves (cranial nerve VI) are normal and are responsible for the appropriate gaze preference noted on the video. Hence options D and E are incorrect.



**Video 2.** Click here to view the video. Reproduced with permission of Akshaya Vachharajani, MD, copyright 2018.

## ACKNOWLEDGMENT

We wish to thank the family and Bryan Camp (Media Services at St Louis Children's Hospital, St Louis, MO) for the production and editing of the video.

## Suggested Reading

Ropper AH, Samuels MA, Klein JP, eds. Disorders of ocular movement and pupillary function. In: *Adams & Victor's Principles of Neurology*. 10th ed. New York, NY: McGraw-Hill; 2014; chap 14. Available at: <https://accessmedicine.mhmedical.com/content.aspx?sectionid=49251501&bookid=690&jumpsectionID=49253960&Resultclick=2>. Accessed March 13, 2019

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- Recognize the clinical features of cranial nerve, cervical root, and brachial plexus palsies, including risk factors.
- Understand the pathogenesis, clinical and imaging features, diagnosis, management, and outcome associated with subdural hematoma.

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**Neonatal Hemophagocytic Lymphohistiocytosis:** 1. A; 2. C; 3. E; 4. E; 5. B.

**Severe Combined Immunodeficiency: A Review for Neonatal Clinicians:** 1. B; 2. E; 3. E; 4. A; 5. D.



**An Infant with Abnormal Eye Movements**  
Maja Herco, Vitaliy Soloveychik and Akshaya Vachharajani  
*NeoReviews* 2019;20:e367  
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# Impact of Nonmedical Factors on Neurobehavior and Language Outcomes of Preterm Infants

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## Education Gap

It is important for health care professionals to understand and address not only the medical risk factors associated with extreme prematurity that affect preterm infant neurobehavior in the NICU and postdischarge outcomes, but also the powerful effects of maternal, NICU, and social environmental risk factors.

## Abstract

Preterm infants are at increased risk for adverse neurodevelopmental outcomes. The impact of maternal, NICU, and social environmental factors on early neurobehavior and language outcomes of preterm infants is recognized. There is a need for health care professionals to have a clear understanding of the importance of facilitating positive mother-infant relationships, and to address not only the infant's sensory and language environment, but also focus on adverse maternal mental health and social adversities to optimize infant outcomes.

## Objectives After completing this article, readers should be able to:

1. Identify characteristics of the NICU environment that contribute to less optimal neonatal neurobehavior and short- and long-term language outcomes.
2. Explain why the development of early language skills is important.
3. Describe the relationship between environmental characteristics and brain development in preterm infants.
4. Identify maternal/parental interventions that should be encouraged in the NICU to improve short- and long-term language outcomes.

## INTRODUCTION

Both biologic factors and a spectrum of environmental factors affect neonatal and postdischarge outcomes of preterm infants. (1) Infants flourish optimally in an

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### ABBREVIATIONS

AAP	American Academy of Pediatrics
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
COPE	Creating Opportunities for Parent Empowerment
EEG	electroencephalography
FICare	Family Integrated Care
IDS	infant-directed speech
MRI	magnetic resonance imaging
NNNS	NICU Network Neurobehavioral Scale
SFR	single-family room



environment that includes maternal comforting touch, voice, and love beginning at birth and continuing in a stable secure home environment. (2)(3)(4) Maternal, NICU, environmental, and socioeconomic factors that are early predictors of neurobehavior and language outcomes of preterm infants have been described. (5)(6)(7)(8)(9) There is a need for health care professionals to have a clear understanding of the importance of facilitating positive mother-infant relationships beginning in the NICU, and the need to address adverse maternal mental health, social adversities, and the infant's sensory environment to optimize outcomes of preterm infants.

## STRESS

Over the past decade, the adverse effects of stress have been well documented and described. Beginning with the landmark Adverse Childhood Experiences Study, (10) researchers started to appreciate not only the short-term but also the long-term negative implications of stress exposure. The repetitive, continuous, or extreme activation of the stress response system is linked to the term "toxic" stress. Risk factors for stress include early abuse, neglect, and parental mental health problems. The American Academy of Pediatrics (AAP) 2012 report on early adversity and toxic stress introduces an eco-bio-developmental framework that affects brain development and subsequent long-term health. (11) The current paradigm proposes that the convergence of genetics, environmental stresses, and developmental outcomes define health.

## THE NICU ENVIRONMENT AND STRESS

By default of being born too early, the preterm infant's new extrauterine environment is an equipment-driven NICU, consisting of multiple, potentially toxic stressors, including reliance on complex technology coupled with separation from the mother. Of great concern is the influence of stress on the development of biologic systems, including the brain, (12)(13) endocrine, (14)(15)(16) and immune systems. (17)(18) The load of stress in the NICU, while lifesaving and necessary, is often chronic or repeated. Direct, early, painful stimuli can include intubations, mechanical ventilation, intravenous catheter placement, and heel sticks. (19)(20)(21) In a 2016 systematic review consisting of 18 observational studies, Cruz et al described an average of 8 to 18 invasive procedures per neonate per day in the NICU. (22) In addition, a rapid change to bright lighting that often accompanies critical procedures may contribute to physiologic dysregulation. (23)

The early infant-caregiver bond that is essential for healthy development is altered in the NICU as a consequence of the medical acuity and environmental constraints. During a period when nurturing is critical, preterm infants are separated from their mothers. Infants in the NICU are therefore deprived of maternal touch and skin-to-skin care.

Innovative animal research from Liu et al demonstrated that rat pups exposed to increased levels of maternal care, characterized by licking and grooming, had improved stress reactions measured by hypothalamic-pituitary-adrenal responses. (15) In humans, benefits of skin-to-skin contact are well documented and have been noted to promote various health benefits, including increased breastfeeding, (24) improved cardiorespiratory stability and growth, (25) and amelioration of procedural pain. (26)(27) For preterm infants in particular, early, consistent, and prolonged skin-to-skin contact has been shown to reduce rates of morbidities, such as bronchopulmonary dysplasia and nosocomial infection. (28) Yet ill infants are not often held because of concerns about adverse medical consequences. (29)(30) Importantly, benefits of skin-to-skin care may also extend to parents, with reports of decreased symptoms of depression and anxiety (31)(32) and more positive parent-child interactions. (33) In a systematic review of barriers to kangaroo care, Chan et al identified several deterrents, including lack of time, support, and family acceptance. (34)

It is important to recognize that while the mother and hospitalized infant are separated from each other physically, there is also a risk of emotional separation. (35) There are myriad reasons that mothers may feel isolated or "removed" from their role as mother. Loss of control, (36)(37) infant appearance and behavior, (38) and frightening NICU sights and sounds (38) may lead to parent withdrawal. Indeed, higher rates of symptoms of depression, anxiety, worry, and posttraumatic stress disorders are reported in mothers of preterm infants compared with mothers of term infants, (39)(40)(41) and some symptoms may start as early as the time of delivery. (42) Poor maternal mental well-being has been associated with decreased visitation, (43) decreased participation in bedside care, (44) and decreased parenting readiness. (45)

## INTEGRATION OF THE FAMILY INTO NICU CARE

Acknowledging parents as key caregivers in the NICU, the National Perinatal Association recommends broadening the mindset of neonatal care to multidisciplinary family care in efforts to buffer acute and chronic NICU stressors. (46)(47)

(48) Sanders and Hall, as well as others, suggest that as trauma is experienced by both infant and parents in the NICU; staff provision of care to families shifts toward trauma-informed care to promote the mother-infant connection and improve the outcome for both the mother and her infant. (49)(50)

Several investigators have not only recognized the need for integrated, family-centered care to potentially buffer the effect of NICU stressors, but have designed interventions or models of care to help facilitate and encourage parental participation. In 2001, Melnyk and colleagues described a NICU-based intervention, Creating Opportunities for Parent Empowerment (COPE), an educational-behavioral curriculum for parents of preterm infants aimed at strengthening parent knowledge, role, and participation in needs and care. (51) Randomized controlled trials incorporating COPE have demonstrated less NICU maternal stress, depression, and anxiety, (52)(53)(54) and increased parent participation in infant care, (53) compared with control mothers. The Mother-Infant Transaction Program, (55) an intervention that teaches parents how to observe their infant's behavioral state and cues and how to facilitate engaging interaction, has also shown promise. Investigators reported improved mother-infant interactions, (55) including better responses to the infant's stress cues, (56) increased breastfeeding, (57) and reduced postpartum depression symptoms, (57) with some benefits persisting into early childhood. (58)(59)(60) A recent meta-analysis identified programs that were multifaceted, centering on integrating psychosocial support, parent education, and infant development support, which showed significant reduction in parental trauma and stress. (61)

Family Integrated Care (FICare), an innovative model that empowers parents to be integral primary caregivers in the NICU, has expanded family-centered care even further. (62) This model, which starts as early as the day of admission, is showing promising results; it teaches parents how to participate in bedside care, enhances staff/parent education, fosters active communication, and implements peer support in a supportive physical environment. (63)(64)(65) In 2018, O'Brien and colleagues reported results of a randomized controlled trial from 26 tertiary NICUs in Canada, Australia, and New Zealand. (66) Mothers in the FICare group, who committed to being present in the NICU for at least 6 hours/day, were compared with those receiving standard NICU care. At day 21, infants in the FICare group had greater weight gain and were more likely to exclusively receive breast milk, and FICare mothers had lower mean scores on anxiety and stress. Data from these different models clearly demonstrate the benefits of broadening the scope of family integration.

## SINGLE-FAMILY ROOM VERSUS OPEN-BAY NICU

With the intent of supporting enhanced family-centered care models, the single-family room (SFR) environment has been adopted in many NICUs. Benefits for preterm infants have included increased rates of breastfeeding (67) (68); reductions in mortality, infections, apnea, and time to full enteric feeds; and decreased length of initial hospitalization and hospital readmissions. (63)(67)(69)(70)(71) A recently published meta-analysis by van Veenendaal and colleagues (72) that included 13 distinct study populations (consisting of 1 randomized trial, 5 nonrandomized trials, and 7 before-and-after studies on relocation to new NICU environments), found that infants in SFR units had a lower incidence of sepsis (relative risk [RR] 0.63; confidence interval [CI] 0.5–0.78) and higher rates of exclusive breastfeeding (RR 1.31; CI 1.07–1.61). (72) There were no differences in mortality, length of hospital stay, growth, or major morbidities.

Greater parent satisfaction has been reported among families in SFR NICUs, including increased privacy, more comfortable surroundings, decreased noise, and opportunities for longer nurse-parent interactions. (67) (73)(74)(75)(76) Lester et al noted that mothers in SFR NICUs reported not only increased satisfaction, but more involvement in their infant's care, including skin-to-skin care, and less stress, compared with mothers in open-bay NICUs. (71) In addition, improved infant growth and decreased number of medical procedures were mediated by increased developmental support and maternal involvement. Intuitively, it seems reasonable that a comfortable, quiet, family-centered private room environment would lead to increased parental presence. In a Norwegian prospective survey study of preterm infants, Tandberg et al found that mothers in SFRs spent significantly more time in the NICU compared with mothers in an open-bay unit (median of 20 hours/day vs 7 hours/day;  $P < .001$ ). (77) However, it is important to note that in the Lester et al cohort, (71) maternal involvement was related to higher socioeconomic status, and in the Tandberg cohort, (77) mothers were in general highly educated, with nearly 80% of the mothers in SFRs being college-educated compared with 70% of those in open-bay units. Although maternal visitation and involvement is critical to the mother-infant dyad, not all parents are able to spend equal amount of time at the bedside. Sociodemographic factors that may limit presence in the NICU include young maternal age, single parent, greater number of children at home, maternal psychologic distress, and economic challenges. (38)(43)(78)(79) Thus, when

implementing interventions or support for both parents and their infants, success will be maximized if stressors and barriers are recognized and addressed.

Very few studies have looked at sustained benefits and outcomes of infants cared for in SFR NICUs. Lester et al identified increased family-centered care, developmental support, and maternal involvement associated with improved 18-month Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) cognitive and language scores. (80) In a larger cohort from the same NICU, Vohr et al reported that at 18 to 24 months of age, SFR NICU was associated with a 2.5-point increase in BSID-III cognitive scores and a 3.7-point increase in language scores compared with open-bay units. (81) However, in separate models based on insurance type, the beneficial effects of SFR remained significant only for infant language scores in families with private insurance. The findings of associations between increased BSID-III scores and high maternal involvement and socioeconomic status may partially explain the contrasting results reported by Pineda and colleagues. (82) In a cohort of infants born at less than 30 weeks' gestation, infants in private rooms had lower language and motor scores, but the authors noted that this cohort had high rates of public insurance and low parental visitation. Although more studies examining long-term neurodevelopmental outcomes are needed to explore how to optimize the NICU environment, most experts agree about the importance of including sensory-appropriate stimuli in the setting of maximizing parental visitation and involvement.

## INFANT NEUROBEHAVIOR AND ENVIRONMENT

Engaging parents in infant bedside care and developmental support brings to light an aspect of development that is not often recognized, or even assessed in the ICU setting. Infant neurobehavior, which in part is a reflection of the relationship between central nervous system functioning and behavioral adaptations to the environment, can offer early insight into a neonate's functional reactions to biologic, sensory, and social stress. Different assessment tools have been used in various NICU settings, one of which is the NICU Network Neurobehavioral Scale (NNNS). The NNNS is a 20- to 30-minute validated, standardized, comprehensive evaluation that incorporates neurologic, behavioral, and stress measures with strong interrater reliability. (83)(84)(85) Certified examiners assess tone, reflexes, items that reflect physical maturity, social/behavioral functions, including auditory and visual orientation, and comprehensive stress signs, which are organized by organ system. Thirteen summary scores are used to summarize the

clinical examination. Much of the early NNNS work centered on term infants, and by providing normative reference values, investigators were able to evaluate term infants in various high-risk medical and psychosocial settings. (86)(87)(88)(89)(90)

More recently, the NNNS has been used in cohorts of preterm infants. Compared with term infants, preterm infants display more nonoptimal reflexes, poorer quality of movements, less attention, and more difficulties regulating stress. (91) However, supportive environments may help optimize neurobehavior. Lester et al reported that preterm infants in SFR NICUs had less lethargy, hypertonicity, and physiologic stress signs, and showed better attention at term-age compared with infants in open-bay units. (71) Findings were mediated by increased maternal involvement and developmental support. Similarly, Pineda et al observed that increased parent holding and skin-to-skin contact was associated with better reflexes and less asymmetry at term postmenstrual age. (78)

As expected, medical complications also have negative effects on neurodevelopment; chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis, and gray and white matter abnormalities seen on magnetic resonance imaging (MRI) have all been associated with abnormal NNNS summary scores. (92)(93) Smith et al reported that increased Neonatal Infant Stressor Scale scores were associated with altered NNNS motor scores. (7) Patterns of summary scores may also be categorized in mutually exclusive "profiles," which represent an overall repertoire of the infant's neurobehavior functioning and interactions. (94) Profiles may be helpful for parents and clinicians to have an overall "picture" of an infant's neurobehavior. NNNS profiles, which can be categorized from most typical (low risk) to most atypical (high risk) have also been useful, because atypical profiles have been shown to be predictive of early childhood motor, cognitive, and behavior problems in a cohort of infants of less than 37 weeks' gestation with prenatal substance exposure. (95)

## NICU LANGUAGE ENVIRONMENT

More recently, social and sensory isolation in the NICU have been recognized as possible contributors to adverse outcomes. (4)(96)(97)(98)(99) Preterm infants in the NICU have multiple caretakers, repeated painful procedures, dependency on complex technology, and absence of continued caretaking by their mothers. (21)(100) The noise environment of the NICU is accentuated by monitors, respiratory equipment, and number of staff. (101) Although the AAP recommends maintaining noise levels at 45 dB,

levels are reported to be consistently higher. (102) Pineda et al reported that the average NICU sound level was 58.9 dB, with an average peak level of 86.9 dB. (8) Noise level was significantly related to medical interventions. The NICU environment can be contrasted with that of the healthy full-term infant who is exposed to typical touch, talk, and social interactions of a family unit and goes home from the birthing hospital in 1 to 3 days. In the Pineda et al study, parent presence and parent holding of the infant in the NICU were both associated with increased adult word exposure. (8)

The question then arises: “Is the infant in the NICU physiologically ready for language exposure?” In fact, auditory reception occurs as early as 24 to 26 weeks of gestation when the cochlea of the inner ear completes development. The fetus responds to vibroacoustic stimuli by 24 to 25 weeks and has consistent responses by 27 to 28 weeks’ gestation. (103) Changes in fetal heart rate in response to maternal voice as early as 32 to 37 weeks’ gestation have been interpreted as a preattention reaction. (104) Three-day-old term infants prefer their mothers’ voice to other female voices. (105)

A study of preterm infants of 25 to 30 weeks’ gestation who were exposed to alternate feedings with exposure to either standard NICU sounds or 30-minute recordings of their mothers’ heart rate and voice identified that the infant’s heart rate decreased significantly in response to maternal sounds. (106) This was interpreted as greater comfort/relaxation of infants when exposed to their mother’s sounds. Other beneficial effects of recorded mother’s voices that have been reported include decreased apnea and bradycardia, (107) increased weight gain velocity, (108) increased attending behavior, (109) earlier enteral feedings, (110) and increased visual attention and quality of movements. (111) Caskey et al reported that very preterm infants in the NICU have vocalizations other than cry, that these vocalizations increase between 32 and 36 weeks’ gestation in the NICU, and that preterm infants vocalize and respond preferentially to their mother’s voice over the nurse’s voice as early as 32 weeks’ gestation. (6)

## LANGUAGE OUTCOMES INCREASED RISK

Language skills are key to successful communication, social-emotional development, and academic success. An extensive body of evidence has demonstrated that preterm infants are at increased risk of short-term and long-term mild to moderate delays in speech and language, (112)(113)(114) including vocabulary development, (115) phonological processing, (116)(117) language

comprehension, (118) verbal short-term memory, (119) and grammatical development. (120) Numerous studies and reviews (121) have reported preterm infant delays and impairments in both simple language function and complex language functions. (112)

Language delays among preterm infants are often found in association with additional cognitive (122) and behavioral challenges. (123)(124) Language delays and impairments in preterm infants have been associated with neonatal illness severity, such as brain injury including grade 3 to 4 intraventricular hemorrhage, chronic lung disease, prolonged assisted ventilation, prolonged hospitalization, and hearing loss. (121) More recently, increased attention has focused on the impact of maternal IQ, adverse mental health, single parent, and non-optimal parent involvement. (125)(126)(127)(128)

## BRAIN AND LANGUAGE

Evidence shows that exposure of the preterm brain to the extrauterine environment alters neuronal differentiation, which may alter subsequent development. (129)(130)(131) The question is then posed: “Does language exposure in the NICU make a difference in brain development and in language outcomes for the preterm infant?” Brain areas of importance for speech and language include the Broca area (both expressive speech and comprehension) in the prefrontal cortex, the auditory cortex and Wernicke area (comprehension), and adjacent parietal areas. Radiographic studies have identified decreased gray matter in the temporal lobes and decreased white matter in the frontal, temporal, and parietal lobes. (132)(133)(134) Very preterm birth is associated with decreased regional brain volumes particularly of the midtemporal cortex, the premotor cortex, and the sensorimotor cortex. (132) Monson et al examined the rates of primary and nonprimary auditory cortex maturation in very preterm infants cared for in either an open-bay or SFR NICU. (135) MRI diffusion parameters of the auditory cortex at term equivalent differed between preterm and term controls. (135) The authors suggest that this reflects either delayed maturation or injury among preterm infants. The preterm infants with disturbed maturation of the nonprimary auditory cortex had poorer 2-year BSID-III receptive and expressive language scores. Room type had no effect.

Variability in outcomes of language studies may be related, in part, to the characteristics of the speech to which the infant is exposed. (136) Infant-directed speech (IDS) also referred to as “parentese,” is more appealing to infants. (137) It is characterized by slower tempo and speech rate, regular

rhythm, higher emotional content, higher pitch and greater pitch range, simplified structure, and acoustic exaggeration of speech sounds, and by the facial expression of the speaker (smiles, raises eyebrows, makes eye contact with the infant). Studies show increased cortical activity in frontal and temporal regions in response to IDS to 12 months of age using both near-infrared spectroscopy and electroencephalography (EEG). In addition, significantly greater activations were elicited in the frontal areas by IDS of the infant's own mother compared with the IDS of unfamiliar women. (137)(138)(139) A study comparing EEG cortical tracking to IDS and adult-directed speech at 7 months of age identified stronger low-frequency cortical tracking in response to IDS. The authors suggest that maternal utterances are important in activating infant brain function and that this process may facilitate early speech processing and language development. (138)

In a report of 40 preterm infants of 25 to 32 weeks' gestation randomized to either maternal sounds (voice and heart rate) or standard NICU sounds during feedings, cranial ultrasonography was performed at 30 days of age. The preterm infants randomized to maternal sound exposure had a significantly larger bilateral temporal auditory cortex, suggesting early brain plasticity, specifically in response to maternal sounds. (140)

MRI scans for neuroanatomic measurements identified regional vulnerability of brain volumes in a cohort of 8-year-old very preterm infants with birthweights of less than or equal to 1,250 g, with the largest decreases observed in the sensorimotor cortex, premotor cortex, and midtemporal cortex. (132) A second study of 8-year-old preterm children reported that those with the lowest verbal comprehension task scores did not fully engage normal semantic processing pathways. Aberrant processing of semantic content may account in part for their lower Peabody Picture Vocabulary Test scores. (141)

## RECOVERY

Evidence shows recovery of language skills with increasing age. In the indomethacin cohort of infants weighing less than 1,250 g, preterm children had continued catch-up on the Peabody Picture Vocabulary Test between 3 and 12 years and gained 1.2 points per year across the study period. Severe brain injury was the strongest predictor of poor language outcomes. (142) Continued assessment at 16 years identified that very preterm adolescents had deficits in higher-order language skills (phonological awareness and phonemic decoding) compared with term controls. (143) Hierarchical growth-curve modeling was used to delineate 4

clusters of cognitive and receptive vocabulary growth among the preterm children. Two clusters of preterm children caught up to term children with increasing age (55% caught up in vocabulary). The children who caught up had lower rates of neurosensory impairment, had more educated mothers, and were less likely to be from an ethnic non-minority. (114)

Nguyen et al described language trajectories of very preterm children compared with full-term controls examined at 2, 5, 7, and 13 years. (144) They identified 5 distinct language trajectory groups using latent growth mixture modeling, allowing for linear and quadratic time trends. The 5 groups included stable normal (32% of cohort), resilient development showing catch-up (36%), precocious language skills (7%), stable low (17%), and high-risk (5%) development. Trajectories that represented poorer language development were present in 40% of very preterm and 6% of term children. Greater social risk was associated with poorer language development with increasing age. The association of lower socioeconomic status with a less optimal language development trajectory with increasing age has been recognized in both term and preterm children. (145)(146)

An example of alterations in functional connectivity was observed in 12-year-old preterm versus term controls in a functional MRI task to examine lexical semantic processing. The preterm and term children performed equally on a semantic association task (identify similar versus dissimilar words). Both preterm and term groups activated regions known to be associated with semantic processing (inferior frontal gyrus and the midtemporal gyrus). However, there were differences in connectivity between regions for both preterm and term children. (147) For the lexical semantic processing task, the left inferior frontal gyrus correlated with accuracy for term children, the left sensory motor areas correlated with accuracy for preterm children, and the left middle temporal gyri correlated with task accuracy for both groups. The preterm and term children overall performed equally well on the task at 12 years, suggesting that plasticity in network connections may provide the opportunity for improving language skills observed with increasing age in preterm infants.

A recent study of term 4- to 6-year-old children reported that both higher socioeconomic status and increased conversations recorded between parents and their child were associated with better language skills. (148) In addition, a higher number of conversation turns between parent and child were associated with increased MRI activation of the left inferior frontal gyrus, a key area for language processing. A mediation model showed that the effect of



conversation turns on language was mediated by the left inferior frontal gyrus activation. The identification of this mechanism of parent-child conversation turns affecting brain activation raises the possibility that early enhanced language enrichment in the NICU can affect the language outcomes of preterm infants.

In the Caskey et al cohort, follow-up of the effects of the NICU language environment identified that increased parent talk with preterm infants in the NICU was associated with higher 7- and 18-month corrected age BSID-III language and cognitive scores. (149)(150) Every increase in 100 adult words per hour at 32 weeks' gestation in the NICU was associated with a 2-point increase in BSID language composite score and 0.5-point increase in expressive communication score at age 18 months. (149) These findings support the importance of parent talk in the NICU as a strong predictor of early infant vocalizations and of language outcomes 18 to 24 months after discharge. It is reassuring that more NICUs are initiating parent reading programs in an effort to enrich the infant's language environment in the NICU. (151)(152) Child-directed conversations beginning in the NICU may be the key to improved preterm outcomes. Addressing family social adversities while infants are in the NICU and encouraging involvement of both parents and NICU staff in providing language nutrition and socialization offers the possibility of improving the language outcomes of preterm infants.

## SUMMARY

Although extreme prematurity and associated medical morbidities remain risk factors for altered neurobehavior, language delays, and impairments, subgroups of preterm infants can improve their language skills with increasing age. Factors in the NICU environment including parent presence, parent caretaking, joint attention, and IDS have positive effects on early language development. Higher level of maternal education, 2-parent households, and other factors associated with higher socioeconomic status are also linked with improving language outcomes. An optimal language environment provided by both parents and staff in the NICU and subsequently in the home can potentially contribute to improved language and school age outcomes. Provision of multidisciplinary support to families and their infants in the NICU, referral of either parent to appropriate support services as needed, and referral of high-risk preterm infants for early intervention services at NICU discharge are recommended to improve outcomes.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the evolution of neurodevelopmental impairments during development and the difference between transient and permanent impairments in NICU graduates (eg, developmental delay vs. intellectual disability; tone abnormalities vs. cerebral palsy)
- Know the effects of socioeconomic factors on the results and generalizability of outcome studies of NICU graduates
- Know the effects of family risk factors (low socioeconomic status, mental health problems) on cognitive outcomes

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1. The landmark Adverse Childhood Experiences Study was the first to demonstrate the adverse effects of chronic stress exposure on long-term health outcomes. Preterm infants admitted to the NICU are exposed to daily stressors; in addition, they experience separation from their mother at a critical period of their development. Which of the following statements regarding the NICU environment and exposure to stress is CORRECT?
  - A. A recent systematic review reported an average of 20 to 25 daily invasive procedures per neonate per day in the NICU.
  - B. Consistent and prolonged skin-to-skin care has been shown to reduce the rates of bronchopulmonary dysplasia and nosocomial infections in preterm infants.
  - C. Concerns for adverse medical consequences are the main deterrent to skin-to-skin care.
  - D. Poor maternal mental health has been shown to lead to decreased participation at the bedside, but not decreased visitation.
  - E. Skin-to-skin care has been shown to ameliorate procedural pain in term infants but not in preterm infants.
2. Family-centered care recognizes the importance of parents as key caregivers for their infant and may be an important avenue to buffer acute and chronic stress in the NICU. Which of the following statements regarding interventions to encourage and facilitate parental participation is CORRECT?
  - A. Family Integrated Care (FICare) is a model of care fostering parent participation as early as the day of admission.
  - B. Improvement noted in the Mother-Infant Transaction Program (MITP) trial did not persist into early childhood.
  - C. The Creating Opportunities for Parent Empowerment (COPE) randomized controlled trial demonstrated improved breastfeeding rates in the intervention group compared with the control group.
  - D. The FICare model requires maternal participation for a minimum of 6 hours weekly.
  - E. The MITP focuses on strengthening mothers' knowledge of breastfeeding techniques and benefits.
3. NICU design plays an important role in facilitating family-centered care. Single-family rooms (SFRs) are increasingly being adopted to support NICU families. Which of the following statements regarding SFR NICUs is CORRECT?
  - A. In a cohort study, Vohr et al (81) reported a 4.5-point increase in Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at 18 to 24 months for infants cared for in an SFR NICU.
  - B. In a Norwegian prospective study, mothers in the SFR NICU spent more time at the bedside, particularly those with lower education level.
  - C. In a recent meta-analysis by van Veenendaal et al, (72) infants in SFR NICUs had increased rates of exclusive breastfeeding and decreased length of stay.
  - D. Pineda et al (82) found lower language and motor scores in a cohort of preterm infants cared for in SFRs.
  - E. The benefits of an SFR NICU are independent of insurance type.

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4. Social and sensory deprivation are now recognized as possible factors in adverse neurodevelopmental outcomes in preterm infants. Which of the following statements regarding the noise and language environment of the NICU is INCORRECT?
- A. Preterm infants exposed to a recording of their mothers' voice have decreased apnea and bradycardia and increased weight gain velocity.
  - B. Preterm infants respond preferentially to their mother's voice over other female voices as early as 32 weeks' gestation.
  - C. Studies indicate that the average sound level in the NICU is typically 45 dB, which meets the 25 dB recommended by the American Academy of Pediatrics; however, there are peaks that can sometimes exceed 100 dB in some instances.
  - D. The fetus demonstrates consistent response to vibroacoustic stimuli by 27 to 28 weeks' gestation.
  - E. Very preterm infant vocalizations increase between 32 and 36 weeks' gestation.
5. Preterm infants are at risk for language delays. Which of the following statements regarding language development and language outcomes in preterm infants is INCORRECT?
- A. Every increase in 100 adult words per hour at 32 weeks' gestation is associated with a 2-point increase in BSID-III language composite score.
  - B. In the indomethacin cohort of infants, no catch-up on the Peabody Picture Vocabulary test was observed between 3 and 12 years.
  - C. Poorer language developmental trajectories are observed in 40% of very preterm infants versus 6% of term infants.
  - D. Preterm infants exposed to more parent talk have higher 7- and 18-month corrected age BSID-III language and cognitive scores.
  - E. Very preterm infants demonstrate deficits in phonological awareness and phonemic decoding at age 16 years.



# Impact of Nonmedical Factors on Neurobehavior and Language Outcomes of Preterm Infants

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# NICU Diet, Physical Growth and Nutrient Accretion, and Preterm Infant Brain Development

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## Education Gaps

1. The NICU diet comprises many macro- and micronutrients, which are critically important to support early brain development in the preterm infant.
2. Measurement and optimization of linear growth and fat-free mass gains may allow for improvement in both cardiovascular health and neurodevelopment.
3. Non-nutritional factors, such as inflammation, influence nutrient accretion, physical growth, and long-term outcomes.

## Abstract

Half of very preterm infants experience neurodevelopmental impairments after NICU discharge. These adverse outcomes result in part from abnormal brain development and injury that occur during the NICU hospitalization. Although many factors influence infant brain development, nutritional determinants are of particular interest because they are highly modifiable within clinical care. Physical growth of preterm infants in the NICU continues to lag behind the reference fetus, suggesting reduced nutrient accretion during a critical period for brain development. Nutrient accretion is driven by intake of specific nutrients such as macro- and micronutrients as well as non-nutritional factors such as systemic inflammation. Most often, anthropometric indicators, such as weight, length, and head circumference, are used as proxies for nutrient accretion. A limitation of weight is that it does not differentiate the healthy growth of specific organs and tissues from excess fat accumulation. Body length provides information about skeletal growth, and linear growth stunting predicts neurodevelopmental impairment. Head circumference is only a crude proxy for brain size. More recently, application of new technologies such as air displacement plethysmography and magnetic resonance imaging has allowed the direct estimation of lean tissue accretion and brain growth in the NICU. These newer techniques can facilitate research to improve our understanding of the links among the NICU diet, inflammation, physical growth, and brain development. These new measures may also be relevant within clinical care

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### ABBREVIATIONS

ARA	arachidonic acid
DHA	docosahexaenoic acid
LA	linoleic acid
MRI	magnetic resonance imaging

to identify infants who may benefit from specific interventions to enhance nutrient accretion and brain development.

## Objectives After completing this article, readers should be able to:

1. Identify specific components of the NICU diet that are linked to improved neurodevelopmental outcomes.
2. Recognize that routine monitoring of linear growth and body composition may facilitate optimized nutritional care and improve long-term health and developmental outcomes.
3. Specify non-nutritional factors such as inflammation that inhibit nutrient accretion, reduce physical growth, and may contribute to poorer neurodevelopmental outcomes.

## BACKGROUND

Despite substantial improvements in survival for very preterm infants in the past 3 decades, these infants remain at heightened risk for impaired neurodevelopment compared with their healthy full-term counterparts. Adverse neurodevelopmental outcomes have many determinants ranging from prematurity-associated brain injury, systemic inflammation and infection, and social factors, but nutritional determinants are of particular interest because they are highly modifiable in the context of clinical care.

A critical window of opportunity for optimizing nutritional care exists during the NICU hospitalization. During this 2- to 4-month period, the brain undergoes extensive structural development including a 3-fold increase in size, formation of all gyri and sulci, the establishment of connections between neurons, and the early stages of myelination. To proceed normally, these developmental processes depend on the availability of macro- and micro-nutrients. Drawing on animal models of undernutrition in the third trimester and on human interventional and observational studies, we recognize 1) the cause-and-effect link between early-life undernutrition and altered brain development; and 2) that altered brain development resulting from undernutrition during this critical period can have an irreversible effect on functioning. (1)(2)

Despite our understanding of the critical importance of nutrition in the NICU, growth outcomes among preterm infants born in the United States continue to lag behind the reference fetus, (3) suggesting gaps in knowledge and

translation. The NICU diet must compensate for nutrient delivery across the placenta, which is prematurely interrupted at the time of birth. Once delivered and absorbed, nutrients accrete into various body compartments including the skeleton, skeletal muscles, organs (including the brain), and adipose tissue. Importantly, nutrient accretion is driven not just by diet but also by non-nutritional factors such as inflammation and physical activity.

The concept of nutrient accretion is helpful in considering approaches to improve nutritional assessment and care in the NICU. To assess the adequacy of nutrient accretion, infant weight at NICU discharge or weight gain from birth to discharge is most commonly used as a proxy. However, weight does not differentiate skeletal, muscle, and organ compartments from adipose tissue, and therefore may be limited in its ability to capture information about “healthy growth” that is most relevant to the developing brain. Gain in body length (linear growth) reflects skeletal growth, and stunting of linear growth during infancy predicts later neurodevelopmental impairment, (4) demonstrating its relevance to neonatal brain development. Direct estimation of body composition (fat mass, fat-free mass) with air displacement plethysmography is now possible for small infants, and emerging research suggests that fat-free mass predicts neonatal brain function better than fat mass. (5) Quantitative magnetic resonance imaging (MRI) can be performed in the NICU to measure the volume of nutrition-sensitive brain regions and provide information about developing micro-structure in relation to diet composition. Electroencephalography-based measures, such as visual evoked potentials,

assess nutrient-sensitive cognitive functions as early as a few months after NICU discharge.

In this review, we will summarize existing and emerging literature on the role of the NICU diet in promoting optimal brain development. We will further develop the concept of nutrient accretion in various body compartments and the relevance of this concept to our understanding of how nutrition influences the developing preterm brain. We will share exciting developments in the field of neonatal nutrition and brain development that we hope will spark further research and inform improvements in nutritional assessment and care.

## PRETERM INFANT DIET: SOURCES OF VARIATION AND ASSOCIATIONS WITH OUTCOMES

The preterm diet comprises parenteral nutrition solutions and lipid emulsions, infant formula, maternal milk and pasteurized donor human milk, multicomponent and modular human milk fortifiers, and micronutrient supplements. The nutrient composition of infant formula and fortifiers is standardized, whereas maternal and pasteurized donor human milk contain variable amounts of nutrients. (6) An infant's intake of specific nutrients depends not just on the content but also on the volume delivered. Both observational studies and randomized trials inform our understanding of how the NICU diet influences short-term brain development and later functional outcomes (Table).

## Macronutrients

Macronutrient fortification is a cornerstone of nutritional support for the hospitalized preterm infant. Inspired in part by animal studies that revealed permanent alterations in brain structure and function following pre- and postnatal malnutrition, Lucas and colleagues undertook a series of large, multicenter randomized trials almost 3 decades ago. (7) Those studies established that preterm formula enriched with calories, protein, and other nutrients was superior to standard term formula as well as donor human milk (8) in promoting weight gain, linear growth, and head growth during the NICU hospitalization. Further, among infants fed formula only (no maternal milk), those who had received preterm formula in the NICU had  $\sim 1/3$  standard deviation higher cognitive scores (not statistically significant) and  $\sim 1$  standard deviation higher motor scores at 18 months' corrected age compared with infants fed standard term formula. (7)

In a follow-up study, when participants were 15 to 16 years old, those who had received the high nutrient preterm formula had higher verbal IQ scores and larger caudate size on MRI than those who received the standard nutrient (term formula or donor breast milk) diet. (9)(10)(11) Despite the limitations of those studies, such as low cohort retention and post hoc comparisons, the results suggest that nutrient-enriched infant formula provided in the NICU has a lasting impact on brain development. Regarding human milk diets, multicomponent fortification is effective in promoting weight gain, linear growth, and head growth in the NICU

TABLE. **Physical Growth and Nutrient Accretion Measures in the NICU that Predict Later Neurodevelopmental Outcomes**

MEASURE	ADVANTAGES	DISADVANTAGES
Weight gain	Inexpensive Easy Accurate	Does not differentiate lean mass accretion from excess fat deposition Correlates with brain growth but nonspecific
Linear growth	Inexpensive Correlates with skeletal growth, may be better proxy for brain growth than weight gain	Requires special equipment (recumbent length board) and training for accuracy
Head growth	Inexpensive	Requires training for accuracy Crude proxy for brain growth
Fat-free mass	More specific for lean mass accretion than weight gain or linear growth May be better predictor of outcomes	Requires specialized, expensive equipment (air displacement plethysmography)
Brain magnetic resonance imaging	Accurate estimate of overall brain size and size of nutrient-sensitive brain regions Information about brain microstructure	Requires specialized, expensive equipment

but data are lacking regarding long-term benefits to neurodevelopment. (12) With both formula and human milk, it is difficult to discern whether macronutrient fortification alone is responsible for growth benefits, because additional minerals and micronutrients are typically provided as well.

Recent studies have taken advantage of MRI as a window into the impact of macronutrient intake on structural brain development in the NICU. In one such study, serial imaging of 49 infants born at less than 30 weeks' gestation revealed that higher intakes of energy and protein in the first 2 weeks after birth were predictive of greater overall brain growth; enhanced growth of nutrition-sensitive structures, such as the basal ganglia and cerebellum; and greater maturation of early myelinating white matter tracts. (13) Given the timing of the nutritional exposure during just the first 2 postnatal weeks, this study suggests that both parenteral and enteral macronutrient provision are important to support early brain development. Another MRI study of 131 infants born at less than 31 weeks' gestation found that cumulative enteral fat and energy intakes during the first month in the NICU predicted larger cerebellar, basal ganglia, and thalamus volumes at term equivalent age, (14) suggesting enhanced growth of these structures. Higher cumulative energy intake was also associated with a measure of microstructure in an early myelinating white matter tract. Taken together, these neuroimaging studies support the concept that protein and energy intakes in the NICU influence brain development during a critical period.

### Long Chain Fatty Acids

During gestation, long chain fatty acids are actively transported across the placenta, supporting high levels of fetal accretion during the third trimester. Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are transferred preferentially compared with linoleic acid (LA) and  $\alpha$ -linolenic acid. ARA plays important roles in cell growth and differentiation, both ARA and DHA concentrate in the central nervous system, and DHA is highly concentrated in the retina. Preterm infants rely on exogenous fatty acid provision after the interruption of maternal-fetal transfer at the time of preterm birth. (15) ARA and DHA levels fall rapidly after birth whereas LA levels increase, likely because of a different balance of fatty acids in parenteral nutrition compared with transplacental transfer. (16) A recent MRI study highlights the potential importance of these changing fatty acid levels for brain development; higher red blood cell DHA levels near birth and near term were associated with larger brain tissue volumes at term and these larger brain tissue volumes in turn predicted better cognitive and motor scores at 36 months. (17) In contrast, higher LA levels predicted lower

white matter volumes. Somewhat unexpectedly, given the strong biologic rationale, randomized trials of DHA- and ARA-fortified formula have yielded little evidence for benefits to neurodevelopment. (18) Despite this lack of evidence, commercially available preterm formulas in the United States are currently fortified with DHA and ARA.

In human milk, DHA is highly variable and its content depends on maternal diet; therefore, maternal supplementation during lactation is a strategy to increase infant intake. In the DHA for the Improvement of Neurodevelopmental Outcome trial (n=657 infants <33 weeks' gestation), lactating mothers were randomized to DHA supplementation versus placebo groups, which resulted in preterm infants being fed high (1% total fatty acids) or standard (0.3% total fatty acids) maternal milk diets. At 18 months, there was no overall difference in Bayley cognitive scores between high versus standard DHA groups but in a preplanned analysis stratified by sex, scores were  $\sim 1/3$  standard deviation higher among girls fed the high DHA diet versus standard; there were no differences in scores by diet among boys. (19) Although these findings suggest a benefit of DHA supplementation in the NICU on 18-month neurodevelopmental outcomes (at least among girls), additional follow-up at school age did not reveal any persistent benefits. (20) Addition of long chain fatty acids to human milk fortifier is another strategy to increase infant intake but has not been rigorously tested in clinical trials with respect to neurodevelopmental outcomes.

### Zinc

Zinc is an essential micronutrient. (21) In the brain, zinc plays key roles in neuronal proliferation, differentiation, and signaling. (22) and is involved with the processes controlling myelination. (23) Altered zinc balance in the brain contributes to neuronal (24) and oligodendrocyte death, (25) suggesting its relevance to preterm brain injury. Preterm infants are vulnerable to zinc deficiency because of their limited stores at birth and compromised absorption. (26)(27) Zinc content varies 10-fold in human milk (28) and some women have extremely low levels of zinc in their milk because of a genetically determined reduction in zinc transfer by the mammary gland. (29)(30) Other sources of zinc in the preterm diet include parenteral and enteral supplements, preterm formula, and multicomponent human fortifier. Infants with severe zinc deficiency have a typical skin rash, failure to thrive, and irritability, but infants with mild or moderate deficiency may not have any clinical symptoms. (26)

Current dietary guidelines suggest an intake of 1 to 3 mg/kg per day for preterm infants, (31)(32)(33) but these



guidelines are based on limited data. In one randomized trial, more zinc (~10 mg/day) was beneficial for linear growth, (34) and in another study, a similar dose reduced morbidity and mortality. (35) Despite these findings suggesting that higher zinc intake may be beneficial for short-term outcomes, no study of very preterm infants in a high-resource setting has examined zinc in relation to long-term neurodevelopment. Because excess zinc intake may interfere with absorption and function of other micronutrients such as copper, (33) an increase in supplementation should be undertaken cautiously. Overall, despite the biological importance of zinc within the developing brain, many data gaps exist with respect to optimal zinc intake for the preterm infant in the NICU.

### Choline

Choline is another essential nutrient that plays important roles in the developing brain. (36) Choline is a precursor of the neurotransmitter acetylcholine and is required for the formation of phosphatidylcholine and sphingomyelin. Choline also influences DNA and histone methylation, which are epigenetic processes that regulate gene expression. Numerous animal studies have demonstrated benefits of choline supplementation during pregnancy on offspring brain development and function, and a few randomized trials of prenatal choline supplementation have demonstrated analogous benefits in humans. (37) In utero, the placenta actively transports choline and thereby provides high amounts of choline to the fetus. In contrast, in human milk, choline is present in variable amounts, and levels are lower in preterm than in full-term milk. (38) Choline is added to preterm infant formula and to some but not all human milk fortifiers. The postnatal fall in plasma choline suggests that the preterm diet does not provide enough choline to match fetal accretion for all infants. (39) However, very little is known about the optimal intake of choline for hospitalized very preterm infants.

### Human Milk

Fortified human milk is the recommended diet for virtually all preterm infants. (40) In addition to medical benefits, such as the prevention of necrotizing enterocolitis, a maternal milk diet in the NICU is associated with enhanced brain development, as seen on MRI, and with improved neurodevelopmental outcomes at school age. (41) Possible mechanisms for this beneficial effect include nutrients and non-nutrient bioactive factors that are present in human milk but not formula, as well as differences in parental caregiving. Paradoxically, fortified human milk-fed preterm infants gain less weight and have less head growth than formula-

fed infants, suggesting lower nutrient accretion despite routine fortification. (42) Human milk-fed preterm infants also accrete relatively less lean mass by the time of NICU discharge than formula-fed infants. (43) One possible reason for these differences in physical growth is that human milk is highly variable in its nutrient composition and may provide cumulatively less protein and/or energy over time for some infants. Pasteurized donor human milk ("donor milk") is even lower in protein than maternal milk and little is known about its micronutrient content. Current human milk fortification strategies presume typical protein, energy, and other nutrient levels in human milk, and do not explicitly differentiate maternal from donor milk. Further, protein and fat levels are uncorrelated, (44) meaning that some infants may receive a high-energy, low-protein diet that encourages the deposition of excess adiposity, whereas others may receive a high-protein diet that encourages accretion of lean mass. Overall, fortified human milk is the recommended diet in the NICU and appears to confer benefit for neurodevelopmental outcomes. However, current fortification practices may not be adequate to support physical growth for all infants because of the variability of nutrient composition in human milk; the extent to which these differences in macronutrient intake influence the developing brain are unknown. Studies of individualized fortification using point-of-care milk analysis in the NICU may be helpful in clarifying short- and long-term effects on brain development.

## ASSESSMENT OF NUTRIENT ACCRETION BY MEASUREMENT OF PHYSICAL GROWTH AND BODY COMPOSITION IN THE NICU

### Physical Growth Assessment with Anthropometry

**Weight Gain.** Current recommendations cite the healthy fetus as the standard to which preterm infant weight gain should be compared (45); however, approximately 50% of very low-birthweight preterm infants are discharged with a weight below the 10th percentile and 30% are discharged with a weight below the 3rd percentile. (3) Because of the ease of accurate measurement, most early literature examining the relationships between physical growth and neurodevelopment focused on weight gain, demonstrating consistently that slower weight gain in infancy is associated with poorer neurodevelopmental outcomes. In one such study of 500 extremely low-birthweight infants born throughout the United States, Ehrenkranz et al found that infants in the top quartile of weight gain (21 g/kg per day) while in the NICU had an 8-fold reduction in cerebral palsy and a 2.5-fold reduction in any neurodevelopmental

impairment at 18 months' corrected age compared with those in the lowest quartile (12 g/kg per day). (46) In another study with 18-month outcomes, in 613 preterm children born before 33 weeks of gestation, faster weight gain before term was associated with higher scores on the Bayley scales (47); weight gain out of proportion to linear growth (increasing body mass index) was also positively associated with neurodevelopment. Regarding adult outcomes in very low birthweight infants in the Helsinki cohort, for each standard deviation faster weight gain before term, performance IQ was higher by 5 points. (48) Associations were also evident between faster weight gain and better executive functioning, visual memory, and verbal flexibility. (48) Overall, these studies demonstrate the importance of weight gain as a growth indicator in the NICU that is relevant for future neurodevelopmental outcomes.

Although the weight gain of the typical fetus is approximately 15 to 18 g/kg per day, this may not be sufficient for preterm infants who need to undergo catch-up growth after an initial period of weight loss or slow gains. Based on the Ehrenkranz et al study, a weight gain velocity of closer to 20 to 30 g/kg per day while in the NICU before reaching term may be necessary to optimize long-term neurodevelopmental outcomes. (46) A limitation of relying on weight gain alone is that it is easily influenced by fluid status, including the significant fluid shifts that preterm infants experience in the first few weeks after birth; often the effect of this early weight loss on the weight gain trajectory is not recovered before hospital discharge. In addition, examining weight gain without considering concurrent linear growth is limited with respect to the balance of excess adiposity gain compared with "healthy" growth of organs and tissues. In conclusion, weight gain is a useful indicator of nutrient accretion in the NICU with direct relevance to neurodevelopmental outcomes, but clinicians should recognize its limitations and consider incorporating other measures to more fully assess the adequacy of nutrient accretion in the NICU.

**Length.** Linear growth is thought to represent lean body mass and protein accretion and often is an underutilized measurement in clinical practice and research. Linear growth and fat-free mass accretion are more closely associated with organ growth and predict later cognitive outcomes. A challenge is that accurate measurement of infant length requires appropriate equipment (recumbent length board) and 2 trained measurers. (49)

In multiple studies of preterm infants, linear growth stunting has been shown to be more severe and prolonged than diminished growth in weight or head circumference. (47)(50)(51) Specifically, linear growth is most severely

depressed at term and 4 months' corrected age for prematurity and remains suppressed to 18 to 24 months' corrected age. (47)(50)(51) When evaluating the relationship between linear growth and later neurodevelopment, Ramel et al found that improved linear growth throughout the first year predicted improved neurodevelopment measured at 24 months using the Bayley Scales of Infant Development among very-low-birthweight preterm infants. (50) Specifically, language scores improved by 8 points for each increase in length z score during the hospitalization, and cognitive scores improved by 5 points for increased growth during the first months to year after hospital discharge. These findings persisted after controlling for weight gain and head growth. (50) Similarly, several other studies of preterm infants have shown relationships between improved linear growth in the first months to years of age and improved motor scores on standardized testing. (47) decreased rates of cerebral palsy, (52) and decreased likelihood of IQ less than 85 in adulthood. (51)

Although fetal growth is often used as the goal for optimal preterm infant growth, linear growth is difficult to measure in utero. Fetal crown-heel length is the best surrogate, and varies from 1 cm per week in early and late gestation to as high as 2 cm per week between 20 and 30 weeks' gestation. (53) Therefore, to be most accurate, linear growth should be measured weekly using a length board and 2 measurers with linear growth goals of 1 to 2 cm per week. Because length continues to be an important marker of brain development, it should be followed closely and optimized when possible, especially before age 4 months but potentially up to age 2 years.

**Head Circumference.** Head circumference is thought to be a marker of brain growth in early infancy and is typically measured weekly in the NICU. Despite relative sparing when compared with weight gain and linear growth, slow head growth has been associated with poorer neurodevelopmental outcomes in multiple studies.

An Austrian study involving more than 250 very preterm infants found positive associations between IQ measured at age 5 years and head circumference measured at multiple follow-up points, including 3, 12, and 24 months, as well as 5 years. (54) The period between discharge and 3 months seemed to be an especially critical time, reiterating the importance of close growth monitoring that continues beyond hospital discharge and is not focused solely on weight gain. Suboptimal head growth, defined as more than 1 standard deviation, but less than 2 standard deviations below the norm was associated with lower IQ as well. (54) In the Helsinki study, similar to weight gain, head circumference gains before term were associated with improved

neurodevelopment, specifically each increase in head circumference z score was associated with a 3- to 8-point improvement in IQ. (48) The authors also found associations between faster head growth and verbal flexibility, visual memory, and executive function. (48) Head growth from term to 12 months' corrected age was less consistently associated with improvements in neurocognitive abilities; however, after controlling for neonatal complications and illnesses, faster head growth in the first year after term was associated with improved IQ. (48) Belfort et al also found improved 18-month Bayley scores with faster head growth before term, but no improvement for more rapid growth after term in infants born at less than 33 weeks' gestation. (47) Fetal head circumference gains are approximately 1 cm per week and correlate with brain growth. Microcephaly has been shown to be associated with loss of gray matter. Also, although head circumference appears to be relatively spared when compared with weight and linear growth, (47)(50) up to 30% of preterm infants continue to have suboptimal head growth (55); this suboptimal growth has been associated with poorer neurodevelopment. (54) Head growth up to 5 years, but particularly before term, is critical for optimizing neurodevelopment. For these reasons, head circumference should be measured at least weekly and if restriction occurs early, catch-up growth should be monitored and optimized with goals of at least 1 cm per week.

### Assessment of Body Composition

Disproportionate weight gain and linear growth has been recognized for some time, but more recently, the availability of equipment allowing direct estimation of body composition in small preterm infants has facilitated a surge of research on the topic. This literature has revealed that preterm infants have decreased amounts of fat-free mass and increased relative adiposity compared with term infants at term corrected age. (50)(56) In addition, the fat mass in this population has a different distribution from that seen in healthy term infants with increased abdominal adiposity and decreased subcutaneous fat. (57) Some evidence suggests that these early differences in adiposity may resolve in early infancy, (58)(59) but the impact of these short-term changes on long-term growth and metabolic health is still poorly understood.

**Fat-free Mass Represents Protein Accretion and Growth of Organs and Tissues.** In a series of small studies, it has been shown that gains in fat-free mass throughout infancy and early childhood among preterm infants are associated with improved development, and that gains in fat mass during these same periods do not confer the same benefit. (5)(60)(61)(62) Specifically, faster gains in fat-free mass

throughout the NICU stay are associated with higher standardized development scores in motor and cognitive domains measured at 12 months of age by the Bayley Scales of Infant Development (5) and faster speed of processing at 4 years of age (measured via visual evoked potentials). (62) In addition, increased fat-free mass gains before discharge from the NICU and throughout the first 4 months after discharge are associated with 1) faster speed of brain processing in infancy and at preschool age (measured via visual evoked potentials at both time points), and 2) improved working memory at preschool age measured via the Wechsler Preschool and Primary Scales of Intelligence. (60)(61)(62) Finally, increased gains in fat-free mass from infancy to preschool age are associated with faster speed of processing and IQ measured on standardized developmental testing at age 4 years. (61) In each of these studies, no improvement in neurodevelopment was found in relation to fat mass gains.

Given that fat-free mass gains are an important predictor of later neurodevelopment and that early fat mass gains may contribute to later metabolic risk, measurement of infant body composition, coupled with practices that enhance fat-free mass gains, may allow optimization of both long-term neurodevelopment and overall cardiovascular and metabolic health.

### NON-NUTRITIONAL INFLUENCES ON PHYSICAL GROWTH AND BODY COMPOSITION

Despite improvements in nutritional care for preterm infants, this high-risk group of children continues to exhibit stunted and disproportionate growth. While this may be secondary to continued inadequate or inappropriately balanced intake, more recently, it was shown that non-nutritional factors may also play a significant role in these altered growth patterns. Growth factors such as insulinlike growth factor 1 act by modulating nutrients into growth and are also important for neuronal growth and differentiation. Without growth factors, cells will not differentiate, even with adequate nutrients. Growth factors are nutritionally regulated and cannot mediate growth without proper nutrient supply, but also have been shown in many pediatric populations to be suppressed by illness and inflammation, likely through increased somatic protein breakdown. Given that premature infants are at risk for both low protein intake and inflammatory states that promote protein breakdown, it is not surprising that they undergo such significant linear growth suppression and decreased fat-free mass accretion.

In part, the role of illness in growth failure is related to restricted nutritional provision to those who are the most critically ill. This can occur for several reasons, including

fear of intolerance leading to a delayed start to enteral feedings and more frequent and prolonged feeding disruptions leading to a longer period to reach full enteral feedings. In addition to delays in enteral feed initiation and advancement, parenteral nutrition is also often limited in the smallest and sickest patients because of intolerance such as hyperglycemia and hypertriglyceridemia. Eherenkranz et al performed a mediation analysis on more than 1,000 preterm infants using days on mechanical ventilation as their marker of critical illness. (63) The authors found that those who were less critically ill received increased amounts of nutrition in their first 3 weeks after birth, grew faster, had a lower incidence of chronic lung disease, sepsis, and death and improved neurodevelopment compared with those who were more critically ill. (63) They also found that these relationships were mediated largely by energy intake during the first week. They concluded that if more nutrition was provided to those infants who were critically ill, their growth and risk for other morbidities would be improved. (63)

Decreased nutritional provision to those infants may not completely explain the degree of long-term stunting these children experience. Uthaya et al found that the primary determinant of increased abdominal adiposity among preterm infants was degree of illness. (57) Multiple clinical surrogates of inflammation, including days requiring antibiotics, oxygen, and steroids, are negatively associated with linear growth up to 2 years of age. (50) Also, preterm infants with higher illness scores on the first day after birth have been shown to have decreased amounts of fat-free mass up to 4 months' corrected age. (50) The lasting impact of these non-nutritional factors, well beyond the period of malnutrition, suggests that alterations may be occurring in the growth hormone axis; however, further research on this is needed.

## CONCLUSIONS

Many nutritional and non-nutritional factors influence physical growth in the NICU, are linked with measures of early brain development, and predict long-term functional outcomes. Weight gain is convenient to measure in the NICU and predicts neurodevelopmental outcomes in childhood and adulthood; however, linear growth and fat-free mass may be more specific than weight as indicators of nutrient accretion into organs and tissues including the brain. Large observational and randomized intervention studies are needed to further establish the best markers of nutritional status in the NICU and to inform interventions that optimize both short- and long-term outcomes. Such interventions may involve increased provision of

macronutrients and/or micronutrients, or supplementation with non-nutrient bioactive factors discovered in maternal milk. In addition, future interventions might target biological pathways that influence nutrient accretion such as inflammation and the growth hormone axis.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how body composition changes during postnatal growth and development and understand the effect of prematurity
- Know the caloric requirements for optimal postnatal growth of preterm and term infants, accounting for caloric expenditures needed for physical activity and maintenance of body temperature
- Know the consequences of feeding preterm infants too little or too much protein
- Know the importance of prenatal and postnatal nutrition on neurodevelopmental outcomes, including the importance of breast milk for brain development

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1. Preterm infants are particularly vulnerable to suboptimal growth and receiving inadequate nutrition in the NICU, which can lead to alterations in brain development. In randomized trials by Lucas and colleagues comparing various nutrition strategies, which of the following led to higher rates of weight gain, linear growth, and head growth during NICU hospitalization?
  - A. Donor human milk.
  - B. Mother's own milk with supplemental vitamins.
  - C. Partially hydrolyzed formula with supplemental iron.
  - D. Preterm formula enriched with calories, protein, and other nutrients.
  - E. Standard term formula with cow milk-based protein.
2. A woman who just found out that she is pregnant is researching the optimal nutrition for herself and the fetus. She enquires about long chain fatty acids and whether she should supplement her diet. Which of the following statements regarding long chain fatty acids is correct?
  - A. Docosahexaenoic acid is highly variable in human milk, and its content depends on maternal diet.
  - B. Docosahexaenoic acid levels increase rapidly after birth for both preterm and term infants, whereas linoleic acid levels fall.
  - C. Linoleic acid is preferentially transferred from the mother to fetus compared with docosahexaenoic acid.
  - D. Long chain fatty acids only reach the fetus via passive transport across the placenta.
  - E. Several studies have consistently shown a positive impact of docosahexaenoic acid on Bayley cognitive score for male preterm infants, but not for female infants.
3. A preterm infant is receiving both parenteral and enteral nutrition. Which of the following statements regarding zinc supplementation for this patient is correct?
  - A. Altered zinc balance in the brain can contribute to neuronal and oligodendrocyte death.
  - B. Infants with mild zinc deficiency present with severe skin rash, acute tubular necrosis, failure to thrive, and irritability.
  - C. The potential for excessive zinc supplementation does not exist, because even preterm infants can easily filter out zinc through the kidneys.
  - D. There is no naturally occurring zinc in human milk.
  - E. Zinc is not compatible with parenteral nutrition intended for preterm infants.
4. An infant born at 28 weeks' gestational age is receiving fortified human milk. Which of the following describes a benefit of this approach compared with non-human milk preterm infant formula?
  - A. Accretion of more lean mass.
  - B. More head growth.
  - C. More weight gain.
  - D. Prevention of necrotizing enterocolitis.
  - E. Reduced requirement for oxygen in the first week after birth.

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5. An infant born at 25 weeks' gestational age is transitioning from parenteral to enteral nutrition. The team is assessing growth and nutrition status. Which of the following statements regarding current standards of growth for preterm infants is correct?
- A. A strategy to be at the 10th percentile of age-matched fetal growth is optimal.
  - B. A weight gain velocity of 20 to 30 g/kg per day while in the NICU may be necessary to optimize long-term neurodevelopmental outcomes.
  - C. Because of the difficulty in measurement and variation in technique among providers, tracking linear growth has not been shown to be of any benefit in clinical practice or in research.
  - D. Preterm infants with higher illness scores on the first day after birth have increased amounts of fat-free mass for several months.
  - E. Slower head growth is usually associated with bronchopulmonary dysplasia, but has no association with neurodevelopment.

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# Gait Characteristics of Children Born Preterm

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## Education Gaps

Preterm birth is associated with high rates of subsequent motor impairments. Walking is a central part of most basic and leisure daily activities; therefore, knowledge of the timing of walking onset and any variation of gait from normal is essential to understand the needs of children born preterm.

## Abstract

Walking is a central skill of daily living. A delay in the onset of walking can be a sign of abnormal motor development. Further, abnormalities in gait can also affect physical functioning. Children born preterm are at significant risk for neurodevelopmental impairments; however, little is known about how preterm birth affects walking. This review describes current evidence of walking in children born preterm with a focus on the age at onset of walking and comparisons of gait characteristics of children born preterm with those born full-term.

## Objectives After completing this article, readers should be able to:

1. Describe the age at onset of independent walking in infants born preterm compared with their full-term peers.
2. Identify infants who may be at increased risk for delayed walking onset.
3. Explain the various aspects of gait characteristics that have been investigated in children born preterm.
4. Recognize when a child born preterm should be referred to a physical therapist for further motor assessments and/or intervention.

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### ABBREVIATIONS

CP	cerebral palsy
DCD	developmental coordination disorder
GA	gestational age
VPT	very preterm
VLBW	very low birthweight

## INTRODUCTION

### Preterm Birth and Motor Development

Children born preterm (ie, <37 weeks' gestational age [GA]) are at significant risk for neurodevelopmental problems ranging from mild motor impairment, such as developmental coordination disorder (DCD) to cerebral palsy (CP). (1)(2) Prevalence of CP among children born preterm ranges from 7 to 82 per 1,000 live births, and increases with decreasing GA. (3) Furthermore, preterm children are

at high risk for mild and moderate motor impairments. (1)(4)(5) Milder motor impairments present in preterm children in early infancy and childhood, persist in adolescence, (5)(6) and influence the child's function and quality of life. (7) Non-CP motor impairment in children born preterm is estimated to range from 19% for moderate motor impairments to 40.5% for mild-moderate impairments including DCD and minor neurologic dysfunction. (8) A recent study has reported an increased prevalence of non-CP impairment in children born preterm from 23% in 1991-1992 to 37% in 2005. (9) Being born very preterm (VPT; <32 weeks' GA) and/or with very low birthweight (VLBW; <1,500 g) presents an even greater risk for motor deficits compared with those born late preterm and/or with normal birthweight. (5)

Walking is fundamental to the development of motor skills in children. A few small studies have examined the onset of walking in children born preterm and suggest that they have a later onset than their full-term peers. Despite the large body of literature about gait characteristics of appropriately developed children born at term and those with significant motor impairments, the evidence investigating gait characteristics in children born preterm is scarce and yet to be synthesized. (10)(11)(12) In this review, we present available evidence from the last 3 decades about the age at onset of walking in children born preterm compared with those born full-term. We also describe the gait characteristics of children born preterm compared with their full-term peers throughout childhood.

## WALKING ONSET

Walking is an inherently complex task that requires the neural control systems to generate highly coordinated movements of the limbs. (13) There are several characteristics that describe walking (14):

- Spatial gait parameters
  - o Step length: Distance between heel contacts of one foot to another
  - o Stride length: Distance between 2 successive heel contacts of the same foot
  - o Step width: Distance between the 2 center lines of the feet
- Temporal gait parameters
  - o Cadence: Stepping rate or "number of steps per minute"
  - o Single support time: Time spent with only one foot in contact with the ground over a gait cycle
  - o Double support time: Time spent with both feet in contact with the ground over a gait cycle
  - o Stride time: Time spent between 2 consecutive contacts of the same foot

- Stride-to-stride variability: Gait fluctuation and variation from stride to stride

For infants, walking begins with a very wide base, fast stepping rate, and variation in the step length and step time from one step to another. As the child grows, and the neurologic system matures, the walking pattern becomes more regular and coordinated, with less step-to-step variation. Understanding the acquisition of motor abilities, including walking, provides insight into an infant's motor development rate and expected motor performance through childhood. (15)

The age by which walking commences is a significant developmental milestone, with delayed walking potentially indicating a neurodevelopmental delay. (16)(17)(18) Although walking attainment ranges from 9 to 18 months of age, (19) the age at onset is an important predictor of later motor impairment. For instance, the onset of walking at 15 months or later has been shown to be a predictor of DCD at 7 years of age. (20)

## WALKING ONSET IN CHILDREN BORN PRETERM

In the last 3 decades, 14 studies have been published in English that investigated the walking onset age in infants born preterm, with the studies ranging in quality from low (15)(16)(21)(22)(23)(24)(25)(26) to moderate (18)(27)(28)(29)(30)(31) using the Newcastle-Ottawa Scale. (32) A description of the participants' characteristics and the age of walking attainment are provided in Table 1. Across these 14 longitudinal studies, 1,436 infants born preterm (mean GA 30.54 weeks, SD 2.74) and 1,317 infants born full-term (mean GA 39.08 weeks, SD 1.33) were included. Two studies recruited only VPT infants (mean GA 28.3 weeks, SD 1.94), (25)(33) and 5 studies recruited only VLBW preterm infants (mean GA 29.76 weeks, SD 2.75; mean birthweight 1,162.15 g, SD 245.65).

A clear definition of independent walking was provided in most of the studies, with the majority of them using 5 consecutive unsupported steps as a definition of independent walking. (16)(18)(21)(22)(23)(25)(29)(30) The definition of independent walking in the other studies ranged from taking 3 unsupported steps (24) to 10 consecutive unsupported steps (28) to walking independently over 5 m. (31) Three studies did not provide a specific definition. (15)(26)(33) In all the studies, walking onset was established through parental report.

A delay in the onset of walking in preterm children was reported in all of the comparison studies with full-term peers, (16)(18)(21)(22)(23)(29)(30)(31)(33) with the exception of 1 study that reported similar onset. (28) Preterm infants



TABLE 1. Characteristics and Findings of 14 Studies on Walking Onset (Corrected Age)

REFERENCE	N	CHARACTERISTICS	PRETERM GROUP		N	FULL-TERM GROUP		ONSET ASSESSMENT	INDEPENDENT WALKING ONSET DEFINITION	PRETERM WALKING ONSET		FULL-TERM WALKING ONSET	
			GA MEAN±SD (WK)	BW MEAN±SD (G)		GA MEAN±SD (WK)	BW MEAN±SD (G)			MEAN±SD (MO)	MEAN±SD (MO)		
Cahill-Rowley et al (33)	69	Inc VPT (GA ≤32 wk) Exc genetic disorders or congenital brain abnormalities	28.6 ± 2.3	NR	41	Inc full-term Exc not walking by 14 mo	39.5 ±1.2	NR	Parent report	NR	13.1±2.6	11.9 ±1.5	
Nuysink et al (25)	90	Inc GA <30 wk Exc chromosomal, genetic, major neurologic or sensory abnormalities	28±1.57	1,064±241	—	—	—	—	Parent report at visits or by email	Five successive steps without support	15.7 <sup>a</sup>	—	
Angulo 2013/ Taiwan	13	Inc preterm with moderate hypo/hypertonia or developmental delay (without CP) Exc congenital, neurologic or genetic disorders Received physiotherapy	29.0 ±4.8	1,465±1012	—	—	—	—	Parent report	Five successive steps without support	14.6±2.3	—	
	15	Received treadmill training	30.8 ±4.8	1,596 ±944							15.1±3.0		
de Souza et al (30)	30	Inc GA ≤34 wk and BW ≤1,500 g Exc neurologic damage, intellectual disability, or sensory deficiency, orthopedic problems, congenital malformations	30.0±2.3	1,178±193	30	Inc GA ≥37 wk and BW ≥2,500 g Exc history of acute and/or chronic prenatal or perinatal hypoxia	39±1.3	3,270±400	Parent report on biweekly calls	Five successive steps without support	13.8±2	12.3±2	

Continued

TABLE 1. (Continued)

REFERENCE	N	PRETERM GROUP			FULL-TERM GROUP			ONSET ASSESSMENT	INDEPENDENT WALKING ONSET DEFINITION	PRETERM WALKING ONSET		FULL-TERM WALKING ONSET	
		CHARACTERISTICS	GA MEAN±SD (WK)	BW MEAN±SD (G)	N	CHARACTERISTICS	GA MEAN±SD (WK)	BW MEAN±SD (G)		MEAN±SD (MO)	MEAN±SD (MO)		
Ana 2012/ Brazil	77	Inc GA <37 wk Exc ≤3 consecutive consultations, OR presence of congenital or chromosomal anomalies, or major neonatal diseases	31.9 (25.7–36.0)	1,505 (590–2,500)	49	Inc singleton, GA 37–42 wk, BW ≥2,500 g Exc abnormal neurologic examination; delayed adaptive, language, or social development; ≤3 consecutive consultations	39.6 (37.1–42.0)	3,178 (2,500–4,020)	Confirmed by monthly evaluation assessments	Five successive steps without support	12.5 <sup>1b</sup> (9.44–15.4)	12.08 (9.8–14.3)	
Karagianni et al (26)	41	Inc GA ≤34 wk Exc genetic or syndromic disease, gross chromosomal abnormalities, or intraventricular hemorrhage Small for GA	32 (26–34)	1,221±328	—	—	—	—	Parent report	NR	13 <sup>a,b</sup>	—	
Volpi et al (15)	143	Inc GA ≤34 wk, BW ≤1,500 g, and absence of neurologic abnormalities Exc <4 consultations in 1st year, neuromotor intervention, sensory deficiency, or conditions compromise development	30±2	1,130±222	—	—	—	—	Parent report at visit every 2 months and calls if unable to attend	NR	12.8±1.9	—	

Continued

TABLE 1. (Continued)

REFERENCE	N	CHARACTERISTICS	PRETERM GROUP			FULL-TERM GROUP			ONSET ASSESSMENT	INDEPENDENT WALKING ONSET DEFINITION	PRETERM WALKING ONSET		FULL-TERM WALKING ONSET	
			GA	MEAN±SD	BW	GA	MEAN±SD	BW			MEAN±SD	MO	MEAN±SD	MO
			(WK)	(G)	(G)		(WK)	(G)			(MO)		(MO)	
Hong 2009/ Taiwan	29	Inc <37 wk Exc congenital abnormalities	29±4	1,200±600	20	Inc GA 38–42 wk Exc perinatal complications	39±1	3,400±500	Parent report on biweekly calls	Five successive steps without support	12.8 <sup>a</sup> (9.8– >18) <sup>b</sup>	11 <sup>a</sup> (10– 14.5)		
Marin 2009/ Spain	694	Inc VLBW (BW <1,500 g), attend follow-up program Exc abnormal neurologic examination or failed to attend follow-up in first few years	29.6±2.89 (2 SD) <sup>c</sup>	1,123±257.8 (2 SD) <sup>c</sup>	1,000	WHO motor development study population ≥37 wk	NR	NR	Parent report at follow-up visits	Five successive steps without support	13.6±2.8 <sup>c</sup>	12.1±1.8		
Jeng et al (18)	29	Inc GA <37 wk, BW <2,500 g Exc congenital or chromosomal anomalies, major neonatal diseases	32±2.7	1,800±600	29	Inc GA 38–42 wk, normal intrauterine growth Status, normal newborn examination	38.8±1.2	3,300±400	Parent report	Five successive steps without support For 3 consecutive days	12.8 <sup>a</sup> (9.8– 16.5)	12 <sup>a</sup> (10– 14.5)		
Jeng et al (21)	22	Inc VLBW (<37 wk and BW ≤1,500 g) Exc congenital/ chromosomal abnormality, and severe cranial ultrasonographic abnormalities	31.1±2.5	1,180±243	22	Inc GA 38–42 wk, AGA, and normal status at birth Exc maternal/ perinatal complications	39.1±3.1	3,298±219	Data recorded within 1 week	Five successive steps without support	14 <sup>a,b</sup>	12 <sup>a</sup>		
Jeng et al (16)	96	Inc VLBW (<37 wk and BW ≤1,500 g) Exc chromosomal absence or genetic anomalies	30.13±3	1,144.3±248.3	82	Inc GA 38–42 wk, normal delivery, and normal newborn examination	39.2±1.1	3,346.5±330.7	Parent report at monthly calls	Five successive steps without support	Median 14 (10–18) <sup>b</sup>	12 <sup>a</sup> (9.5– 16)		

Continued

TABLE 1. (Continued)

REFERENCE	PRETERM GROUP			FULL-TERM GROUP			INDEPENDENT WALKING ONSET DEFINITION	PRETERM WALKING ONSET		FULL-TERM WALKING ONSET	
	N	CHARACTERISTICS	GA MEAN±SD (WK)	BW MEAN±SD (G)	N	CHARACTERISTICS		ONSET MEAN±SD (MO)	ASSESSMENT	ONSET MEAN±SD (MO)	MEAN±SD (MO)
de Groot et al (31)	33	Inc low-risk preterm  Exc major neonatal diseases or neurologic disorders	30.6 <sup>a</sup> (27.1-34.4)	1,536 <sup>a</sup> (765-2370)	19	Inc GA 38–42 wk with appropriate BW for GA  Exc abnormal examination at age 1 wk	Five successive steps without support	15.77±1.6	Parental report by call + visit to confirm 14 days later	14.3±1.98	
Cioni et al (28)	25	Inc low-risk preterm (<37 wk)  Exc abnormalities or neurologic disorders in 1st year	33.8±2.7	2,100±600	25	Inc GA >37 wk  Exc pre- or perinatal complications, or abnormal examination at birth or 1st mo	Ten successive steps without support	12.2±1.2	Parent report	12.6 ±1.6	

AGA=appropriate for gestational age; BW=birthweight; CP=cerebral palsy; Exc=exclusion criteria; GA=gestational age; Inc=inclusion criteria; NR=not reported; VLBW=very low birthweight; VPT=very preterm; WHO=World Health Organization.

<sup>a</sup>Median.

<sup>b</sup>Not all participants were walking at the end of follow-up.

<sup>c</sup>Data obtained from authors.

attain walking (mean 13.67 months, SD 1.12) at an older age compared with their full-term peers (mean 12.24 months, SD 0.83) (Fig).

Mean walking onset was significantly later (mean 1.43 months; 95% confidence interval [CI] 0.59–2.28) for preterm infants compared with full-term infants (Fig). From studies limited only to VPT and/or VLBW infants, attainment of independent walking for the preterm group was further delayed, compared with full-term children, by approximately 2 months (VPT mean 2.16 months, 95% CI 0.47–3.85; VLBW mean 1.98 months; 95% CI 1.0–3.0) (Fig).

When interpreting the data, it is important to note the follow-up period. In the majority of studies, children born preterm were followed to at least 18 months to assess walking onset age; however, not all children were able to walk by 18 months. (16)(21)(22)(26)(29) Interestingly, 26 children born preterm did not achieve walking by age 18 months and were excluded in these studies. (16)(21)(22)(26)(29) The exclusion of these nonambulant children born preterm might underestimate the actual delay in the age at onset of walking. However, it is also possible that neurologic impairments such as CP may have been identified later in the development of these children. In comparison, all children born full-term walked by 18 months, except in 1 study, which followed full-term infants to 14 months and excluded children who did not walk by this age. (33)

## GAIT DEVELOPMENT IN CHILDREN

Understanding the timing of gait changes and how gait relates to other neurologic and behavioral events provides information about the primary mechanisms of childhood

development. (34) The gait pattern of children continually changes and develops with age throughout childhood and adolescence. (35) Gait is not a constant because it fluctuates from step to step, also known as gait variability. Some evidence suggests that gait development continues to be refined until the underlying pattern becomes mature, at age 7 years. (35) However, cumulative evidence suggests that the gait continues to stabilize throughout childhood and adolescence. (13)(36)

Spatiotemporal parameters measure the time and distance characteristics of gait, (34) and are sensitive indicators to detect gait abnormalities. (14)(34) As noted earlier, spatial gait parameters include measures of step size and stride length while temporal gait parameters include cadence and double support time. (14) These spatiotemporal parameters are associated with changes related to growth and walking experience. (37) For instance, in the months following the attainment of independent walking, there is an increase in walking speed, stride length, and single limb support time, as well as a decrease in the cadence and double support time. (38) As the child continues to grow, further developments in the spatiotemporal characteristics of gait occur with changes in the size of the child's body segments. (37) Therefore, while many parameters reach maturation by the age of 3 to 4 years, speed, cadence, single leg stance, and step length continue to change with increasing age and leg length. (34)(37) Cadence measures in 7-year-old children are still 26% higher than the normal values of healthy adults. (38) Stride-to-stride variability and stride time values are also reported to continually change until age 14 years. (13) Spatiotemporal gait parameters are a valid and reliable method for assessing gait in children, (39)(40) and are sensitive measurements to assess for gait abnormalities. (37)

Kinetic and kinematic measures are also important parameters to consider when assessing the gait of children. Kinetic measures assess the forces generated across the joints during walking, whereas kinematic measures assess joint movements. Kinetic measures are reported to continually alter throughout childhood with evidence showing changes until age 9 years. (34) Comparatively, kinematic measures are reported to stabilize earlier in childhood, with major changes in joint angles occurring between 1 and 2.5 years of age, followed by minimal changes up to age 4 years. (37)

In addition to walking as a single task activity, the ability to perform additional concurrent activities such as talking, carrying objects, or thinking is part of everyday function, and of interest across childhood. Dual-task activities require the person to maintain constant

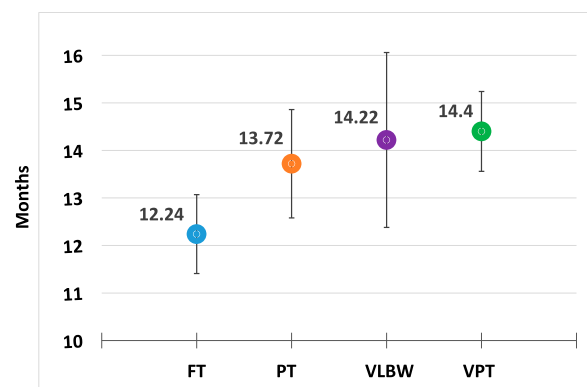


Figure. Age at onset of walking in months, mean  $\pm$  standard deviation. FT=full-term; PT=preterm; VPT=very preterm; VLBW=very low birth weight.

performance of a task while performing additional tasks such as a cognitive or motor task. (41) Dual-task walking has an influence on the gait characteristics of children, including those who are developing appropriately. (42)(43) Not surprisingly, dual-task walking conditions have greater influence on the gait of children with attention and executive function problems at school age. (44)

### Gait Assessment

Gait assessment provides important clinical data for assessing function and determining intervention goals, as well as monitoring the result of medical treatment. (14) To assess a child's gait pattern and identify variation in gait characteristics, it is essential to use normative or reference gait data sets of full-term children who are developing appropriately. (36)(37) Different techniques are available to minimize the variability of gait data by accounting for height and leg length differences and including conventional normalization with body mass. (34) With advances in technical assessments, spatiotemporal gait characteristics can be calculated through instrumented walkways. (33) Similarly, kinetic and kinematic parameters can be derived from 3-dimensional motion systems and force platforms. (33)

## GAIT CHARACTERISTICS OF CHILDREN BORN PRETERM

All 6 studies comparing spatiotemporal, kinematic, and/or kinetic gait characteristics of independent walking among 244 children born preterm (mean GA 30.62 weeks, SD 2.45) and 179 children born full-term (mean GA 39.08 weeks, SD 1.23) are summarized in Table 2.

### Gait Characteristics from Instrumented Assessment

In the studies summarized in Table 2, different instrumented gait assessment tools were used to assess the gait of children, including the GAITRite electronic walkway system (CIR Systems, Inc., Sparta, NJ), (33)(43) a Balance Master computerized force plate (NeuroCom, Clackamas, OR, USA) (27), and kinematic analysis with reflective markers. (18) Step width was significantly wider in preterm children (mean 10.4 cm, SD 2.2) compared with their full-term peers (mean 9.4 cm, SD 1.5) at 18 to 22 months of age. (33) Similarly, stride length was significantly shorter in preterm infants (mean 54 cm, SD 6) compared with their full-term peers (mean 57 cm, SD 7) at age 18 months. (18) All studies were of high (18) or moderate quality (33)(43) using the Newcastle-Ottawa Scale. (32)

When describing gait characteristics in preterm children who were not diagnosed with CP but had mild to moderate developmental delay based on their Bayley Scales of Infant Development, 3rd edition, scores, 1 study found that children born preterm had a significant increase in step width (mean 11.0 cm, SD 3.0) compared with full-term children (mean 9.4 cm, SD 1.5); increased step length asymmetry (mean 0.12 cm, SD 0.1) compared with full-term children (mean 0.05 cm, SD 0.04); and longer step time (mean 0.39 s, SD 0.11) compared with full-term children (mean 0.34 s, SD 0.04). (33) In contrast, there were no significant differences between gait characteristics of children born preterm and their full-term peers when they were walking at a self-selected speed and walking directly on a line at age 7 years, (27) and walking while doing a concurrent task at 9.5 years of age. (43) There was a trend of increased gait variability when walking while doing a concurrent activity for VLBW children compared with full-term peers. (43)

### Gait Characteristics from Observational Assessment

Gait characteristics have also been described in 2 studies using observational gait assessment determined by 2 assessors. (28)(31) The authors described gait characteristics of children during the first few weeks after walking and they found no differences in gait characteristics between children born preterm and those born full-term. (28) The other study, a high-quality study that used an observational assessment tool with a scoring system to assess independent walking, found that children with lower birth GA and birthweight were overrepresented in the near-poor and poor scores. (31)

In conclusion, limited evidence was available for whether and how the gait of children born preterm differs from children born full-term, and importantly, whether any differences persist. The available evidence concentrates on 2 distinct periods, the first few months after the child attains walking and school age. Furthermore, the finding of gait characteristics should be interpreted with caution as a result of the small number of participants; wide GAs and age range of participants at assessment time points; and the variability of the spatiotemporal characteristics tested in the studies. Furthermore, the variable methodologic quality and study design of the included studies need to be considered.

## CLINICAL RECOMMENDATIONS

The onset of independent walking is most commonly defined as the time when an infant can take 5 successive



TABLE 2. Characteristics and Findings of 6 Studies on Gait Characteristics

REFERENCE	AGE	PRETERM GROUP			FULL-TERM GROUP			ASSESSMENT					
		CHARACTERISTICS	GA MEAN±SD (WK)	BW MEAN±SD (G)	N	CHARACTERISTICS	GA MEAN±SD (WK)	BW MEAN±SD (G)	TOOLS AND CONDITIONS	GAIT CHARACTERISTICS	CS	MAIN FINDINGS	
Cahill-Rowley et al (33)	18–22 mo <sup>a</sup>	81	Inc VPT Exc genetic disorders or congenital brain abnormalities Exc 1 infant walked with assistance	28.6±2.3	NR	43	Inc appropriately developing Exc parent gait concerns or walked >14 mo	39.5±1.2	NR	GAITrite Pref walk	Speed, cycle time, step width, step length, and time asymmetry; stance % single support % and double support %	CS	Wider step width in preterm children; longer step time and higher step length asymmetry in preterm children with low gross motor scores
Hagmann-von Arx 2015 (43)	9.5 y	44	Inc VPT Exc M-ABC <16th percentile and low IQ	30.1±2.1	1,423±421	44	Inc GA >37 wk Exc M-ABC <16th percentile and low IQ	39.6±1.5	3,353±429	GAITrite Pref and dual-task walks	Speed, cadence, stride length, single and double support time, SW, SLV	CS	Higher variability in VLBW in dual-task conditions SW and SLV significant for prematurity
Kluenter et al (27)	7 y	44	Inc infants with VLBW Exc major neurologic disorders	28.6 <sup>b</sup> (23.4–34.1)	1,095 <sup>b</sup> (380–1,480)	21	Inc healthy FT from Department of Otorhinolaryngology Exc abnormal otolaryngology or vestibular status, or major neurologic disorders	NR	NR	Balance master Pref and line walks	Step width, step length, speed, and the step length symmetry		No significant differences
Jeng et al (18)	18 mo <sup>a</sup>	29	Inc GA <37 wk, BW <2,500g Exc congenital or chromosomal anomalies, major neonatal diseases	32±2.7	1,800±600	29	Inc GA 38–42 wk, normal growth status, normal newborn examination	38.8±1.2	3,300±400	Kinematic analysis Pref walk	Stride length, stride period, stance time, swing time, interjoint coordination, and interlimb coordination	CS	Shorter stride lengths in preterm children Speed slower in preterm children (not significant)
de Groot et al (31)	14 d <sup>a</sup> after onset	33	Inc low-risk preterm Exc major neonatal diseases or neurologic disorders	30.6 <sup>b</sup> (27.1–34.4)	1,536 <sup>b</sup> (765–2,370)	19	Inc GA 38–42 wk with appropriate weight for GA Exc abnormal examination at 1 wk	39.1 <sup>b</sup> (38.1–41.4)	3,320 <sup>b</sup> (2,960–4,000)	Videotape 2 assessors Pref and fast walks	Step width and asymmetry		Preterm children with lower GA and small for GA overrepresented in near-poor and poor scores
Cloni et al (28)	3–4 wk <sup>a</sup> and 4 mo <sup>a</sup> after onset	25	Inc low-risk preterm, GA <37 wk Exc abnormalities or neurologic disorders in 1st year	33.8±2.7	2,100±600	25	Inc GA >37 wk Exc pre/perinatal complications, or abnormal examination at birth or first months	38.4±1	3,100±300	Videotape 2 assessors Pref walk	Base of support, asymmetry, and foot-strike asymmetry		Asymmetry more in FT (12/25) than preterm children (6/25) not significant

BW=birthweight; CS=correct for body size; Exc=exclusion criteria; FT=full-term infants; GA=gestational age; Inc=inclusion criteria; NR=not reported; M-ABC=Movement Assessment Battery for Children; Pref walk=walking at self-preferred speed; SLV=stride length variability; SW=stride velocity variability; VLBW=very low birthweight; VPT=very preterm.

<sup>a</sup>Corrected for prematurity.

<sup>b</sup>Median.

steps without support. We believe that this definition should be standardized in clinical and research practice to ensure effective communication between professionals and families. Because the age at onset of walking provides insight into a child's motor development and expected motor performance, a child born preterm with a delayed walking onset of more than 14 months should be monitored closely because the average walking onset age in this population is 13.67 months. Children who fail to attain walking by the age of 18 months (which is the normal upper limit for walking onset) should be referred to physical therapy for motor assessment. Further attention should be directed to children born VPT and/or with VLBW because they are at higher risk of experiencing delays and variations in gait. Children born preterm, who have functional difficulty with walking in daily life, need to be referred to health professionals who are trained in gait assessments.

Although there is no clear evidence on how we can facilitate and train children born preterm to improve their gait, there is evidence that early intervention can benefit the motor outcomes of children born preterm. (45) Furthermore, there is emerging evidence that intervention to facilitate walking onset including treadmill training might be of benefit. (24)

## CONCLUSION

This review highlights that children born preterm walk at least 1 month later than those born full-term. The 1-month gap in walking onset increases to more than 2 months when limited to children born VPT and/or with VLBW compared with infants born at term. This delay in walking onset is found in children born preterm without known neurologic impairments such as CP. Further research is needed to understand the relationship between delayed onset of walking and long-term developmental problems in children born preterm. It is also unclear whether affected children catch up later or continue to have issues.

Despite the large body of literature describing the gait characteristics of children born at term who are developing appropriately and those with significant motor impairments, the evidence of gait characteristics in children born preterm is scarce. The available evidence solely concentrates on the first few months after the child attains walking and at school age, while the gait of preschool age children born preterm has not yet been investigated. In the first few months after the onset of walking, up to 22 months of age, children born preterm

appear to walk with wider step width and shorter step length, and those with mild to moderate motor delay have increased step length asymmetry and longer step time compared with children born at term. However, it is not clear if these differences persist as children reach preschool and school age. Dual-task walking conditions are a potential area of challenge for children born preterm and, to date, evidence suggests that preterm children at school age have a higher degree of gait variability compared with their full-term peers. Further prospective studies that investigate the gait of children born VPT and/or with VLBW are warranted. There is also a gap of knowledge in whether the early differences in gait resolve with age and greater walking experience. Understanding the development of the gait of children born preterm is important because walking is a critical daily task that influences the child's general function, academic performance, self-esteem, and participation.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the risks of neurodevelopmental impairments in term infants, late preterm infants, moderately preterm infants, and extremely preterm infants, with and without neurologic risk factors.

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# Index of Suspicion in the Nursery

## 1 A Blueberry Muffin Rash Complicated by Cardiomyopathy

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### PRESENTATION

A 2.4-kg male infant is born at 35 weeks and 3 days of gestation via cesarean section to a 26-year-old gravida 3, para 1 woman whose pregnancy is complicated by dichorionic, diamniotic twins, preterm labor, and decreased variability of fetal heart rate. Maternal serologic findings are normal, other than a nonimmune rubella status. Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. He is transferred to the NICU because of hypoglycemia, which is corrected with dextrose infusion. His female twin sibling has an uneventful newborn course.

Initial examination is unremarkable except for multiple scattered, nonblanching, purple nodules, and macules (Figs 1 and 2), each measuring approximately 5 mm, found on the face, torso, arms, and legs with sparing of the palms and soles and hepatosplenomegaly.

### LABORATORY STUDIES

Rubella titers (IgG 16.5 IU/mL, IgM <20 IU/mL) suggest passive maternal immunity and no evidence of current infection. Urine cytomegalovirus is negative. A complete blood cell count demonstrates leukocytosis of 45,000/ $\mu$ L ( $45 \times 10^9$ /L) with 12% blasts, 11% polymorphonuclear neutrophils, 14% lymphocytes, and 48% monocytes. Complete blood cell count at 24 hours confirms a white blood cell count of 88,000/ $\mu$ L ( $88 \times 10^9$ /L) with similar differential.

### DISCUSSION

#### Differential Diagnosis

These results focused the differential diagnosis on hematologic causes, including congenital acute myeloid leukemia (AML), juvenile myelomonocytic leukemia, and transient myeloproliferative disorder. Bone marrow biopsy revealed a marked increase in monocytic cells, with atypical and immature forms, and 51% blasts. Flow cytometry showed an abnormal blast population with expression of myelomonocytic antigens with aberrant features, including loss of CD13 and CD14, and CD56 expression.

#### Actual Diagnosis

The infant was diagnosed as having congenital AML with monocytic differentiation.

#### Patient Course

Induction chemotherapy was administered using the protocol of the Children's Oncology Group AAML1031, which includes a low cumulative dose of

**AUTHOR DISCLOSURE** Drs Schiff, Supples, Walsh, Russell, and Pylipow have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Characteristic blueberry muffin rash on lower extremity.

daunorubicin ( $67.97 \text{ mg/m}^2$ ). Bone marrow biopsy after induction showed minimal residual disease, a favorable prognostic sign. Prolonged marrow suppression, however, precluded further chemotherapy. The infant's course Lucrezia was complicated by respiratory failure, subglottic stenosis requiring tracheostomy, and anthracycline-induced cardiotoxicity.

Pretreatment echocardiography demonstrated a structurally and functionally normal heart. By 2.5 months of age, he developed an increasing oxygen requirement and pulmonary edema. Echocardiography revealed moderately depressed left ventricular (LV) function (shortening fraction [SF] 20%) and LV dilation. His B-type natriuretic peptide (BNP) reached  $950 \text{ pg/mL}$  ( $950 \text{ ng/L}$ ; normal  $<100 \text{ pg/mL}$  [ $100 \text{ ng/L}$ ]).

The infant's heart failure was initially managed with furosemide and milrinone. At 4 months, he made a transition to an oral regimen of enalapril, furosemide, and spironolactone with stable echocardiographic findings of



Figure 2. Characteristic blueberry muffin rash on torso.

moderate to severely depressed LV function (ejection fraction [EF] 30%, SF 15%).

At 1 year, a mild recovery of function was seen (EF 47%, SF 23%, BNP of  $75 \text{ pg/mL}$  [ $75 \text{ ng/L}$ ]), but by 13 months of age he developed overt heart failure in the setting of a viral illness (BNP of  $4,889 \text{ pg/mL}$  [ $4,889 \text{ ng/L}$ ], and Lucrezia alanine aminotransferase of  $2,067 \text{ IU/L}$  [ $34.5 \text{ } \mu\text{kat/L}$ ] with moderate to severely depressed biventricular function. He was evaluated as a candidate for heart transplantation. Because of worsening heart failure, he was placed on a biventricular assist device at 22 months of age. Despite aggressive cardiac support, he developed worsening pulmonary edema and renal failure requiring venoarterial extracorporeal membrane oxygenation (ECMO). He went on to develop multiorgan failure and ECMO was withdrawn. Remarkably, even up until his death at 23 months of age, his AML was in remission, despite having received an incomplete course of chemotherapy.

### The Condition

Leukemia is the most common pediatric cancer, with AML representing 20% of cases. (1) Current AML treatments achieve 60% to 70% survival but relapse rates approach 50% (2) and survivors often experience treatment-related morbidity, particularly cardiotoxicity. (1) Congenital leukemia is rare ( $<1\%$  of childhood leukemias) but has the highest mortality rate of all neonatal malignancies. AML represents half to two-thirds of congenital leukemias. (2) The most common subtypes are monocytic, myelomonocytic, and megakaryocytic.

Congenital leukemia is defined by presentation in the first 4 weeks after birth; proliferation of immature myeloid, lymphoid, or erythroid cells, with infiltration into extra hematopoietic tissues; and the absence of another diagnosis producing a leukemoid reaction. (3) AML is more common in male infants (2:1) (3) and typically presents with hepatosplenomegaly and infiltration into skin known as leukemia cutis or "blueberry muffin" rash. Lesions are palpable red, purple, or blue cutaneous nodules or macules containing leukemic cells. Central nervous system involvement is less common than with acute lymphocytic leukemia (ALL). Leukostasis and bleeding from thrombocytopenia lead to central nervous system and pulmonary complications. (2)

Congenital leukemia is cytogenetically distinct from leukemia in older children. Neonatal cases possess a rearrangement of the mixed-lineage leukemia (*MLL*) gene located at chromosome 11q23. *MLL* gene rearrangements are observed in 80% of ALL cases and 60% of AML cases diagnosed in the first year after birth. (3) It is believed that most cases of neonatal and infant leukemia arise in utero, sometimes causing fetal hydrops. Risk factors have not been delineated. (3)

Although congenital ALL has a poor prognosis, AML survival in infants nears that of older children. (2) Treatment regimens for AML have a backbone of cytarabine and anthracyclines, with stem cell transplantation for those with high-risk features. (1) Unfortunately, there is significant risk for anthracycline-induced cardiomyopathy, which correlates closely with the cumulative dose. (3) The current patient developed cardiotoxicity despite a low cumulative dose of daunorubicin, perhaps because of risk factors such as young age (<4 years old) and low weight. Cardiotoxicity develops from the accumulation of toxic anthracycline metabolites, and the production of reactive oxygen species. Three forms of cardiotoxicity are described, including immediate pericarditis/myocarditis, early-onset progressive congenital heart failure, and late-onset cardiotoxicity developing years later.

Genetic factors are being identified. (4) Patients with the GG allele on the *CELF4* gene have a 10-fold increased risk of cardiomyopathy over patients with GA or AA genotypes. (5) Carbonyl reductase (CBR) polymorphisms modify the dose-dependent risk. Patients with the CBR3 GG allele, have increased risk despite low- to moderate-dose anthracyclines. (4) Testing for these alleles is not yet commercially available. In transgenic mice, upregulating the carboxyl terminus of heat shock protein 70-interacting protein (CHIP) offers some protection. (6) As genetic testing becomes available, high-risk patients may be identified and receive tailored therapy.

Dexrazoxane, a free radical scavenger, attenuates anthracycline-induced cardiotoxicity, but concerns remain that it may also protect tumor cells from chemotherapy. One randomized control trial suggests that cardiac injury is reduced without compromising antileukemic efficacy (6) and another retrospective cohort study showed no increased risk of relapse. (7)

Trials addressing the management of anthracycline-induced cardiomyopathy in children are lacking. Angiotensin-converting enzyme (ACE) inhibitors, because of afterload reduction, can protect against hypertrophic remodeling. Treatment of symptomatic heart failure includes diuretics, digoxin, and afterload-reducing agents, such as angiotensin-receptor blockers and ACE inhibitors. Mechanical circulatory support serves as a bridge to cardiac transplantation. (8)

### Lessons for the Clinician

- Although rare, AML has higher mortality than neuroblastoma, the most common neonatal malignancy.

- Presentation of congenital AML (up to 4 weeks of age) typically presents with hepatosplenomegaly and/or leukemia cutis caused by leukemic infiltration.
- Anthracycline-induced cardiomyopathy is a common complication of chemotherapy for AML.

## American Board of Pediatrics, Neonatal-Perinatal Content Specification

- Know the clinical and laboratory features of congenital leukemia

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**Case 1: A Blueberry Muffin Rash Complicated by Cardiomyopathy**  
Andrew F. Schiff, Sarah P. Supples, Michael J. Walsh, Thomas B. Russell and Mary  
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# Index of Suspicion in the Nursery

## 2 Dilated Stomach in an Infant with Failure to Thrive

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### PRESENTATION

A 2-month-old male infant undergoes anoplasty for low anorectal malformation. At follow-up, his weight gain is found to be inadequate. However, he is feeding well, his urine output is noted to be adequate, and he has no diarrhea or constipation. Neoanus is healthy and functioning normally. He has no history of vomiting or abdominal distention. Lactation counseling is given and the infant's family is advised to bring him in for regular follow-up for growth monitoring. However, his parents bring him in for a follow-up at 4 months of age because he had been admitted to an outside hospital for pneumonia at age 3 months. His investigations during pneumonia admission are reviewed. Chest radiography shows right upper lobe consolidation with a hugely dilated stomach (Fig 1). There is no history of cough, choking, or blue discoloration of the skin while feeding. There is no history of abdominal distention or vomiting.

On examination, his heart rate is 120 beats/min and respiratory rate is 28 breaths/min. The respiratory system, cardiovascular system, and abdominal examination findings are normal.

Routine blood investigations are normal. Upper gastrointestinal contrast study shows dilated stomach, normal-caliber duodenum with easily emptying stomach, and no evidence of gastroesophageal reflux. Pull-up esophagogram reveals no fistulous communication with the esophagus.

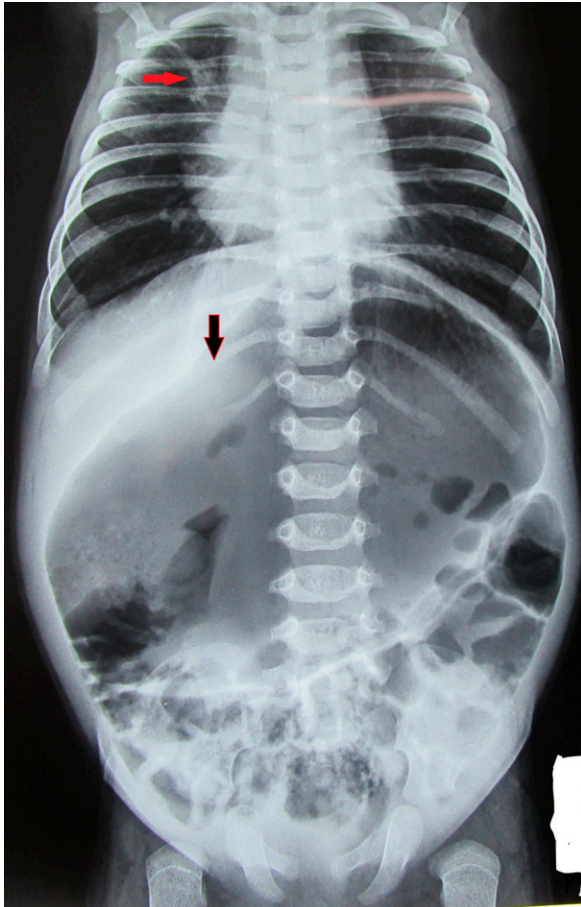
### DISCUSSION

#### Differential Diagnosis

The causes for the dilated stomach in an infant with anorectal malformation with failure to thrive can be gastric outlet obstruction secondary to pyloric stenosis, duodenal stenosis, or gastric volvulus; or an H-type tracheoesophageal fistula may be responsible. The presence of respiratory tract infection in the infant led to a high degree of suspicion of H-fistula even though there was no associated cough or choking episodes while feeding. Upper gastrointestinal contrast study ruled out gastric outlet obstruction, which further strengthened our suspicion of H-fistula even with the normal pull-up esophagogram. Bronchoscopy is the investigation of choice for H-fistula, which helped us diagnose the condition even without the classic presentation.

**AUTHOR DISCLOSURES** Drs Radhakrishna, Parashar, Goel, and Santhanakrishnan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





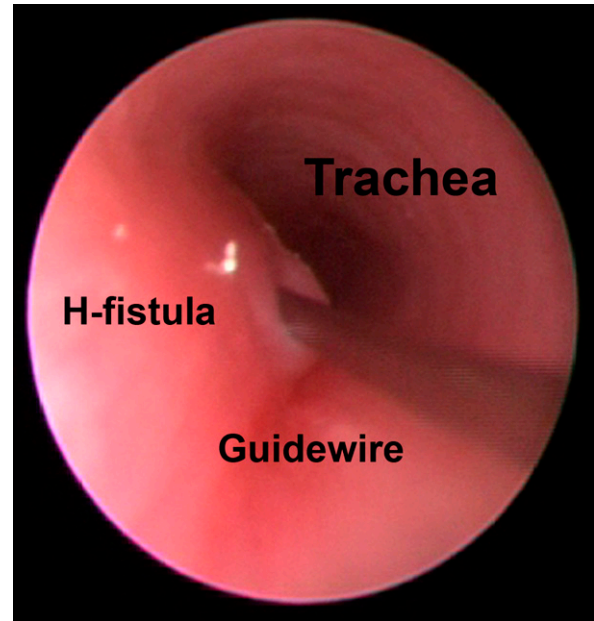
**Figure 1.** Radiograph of the chest and abdomen showing right upper lobe consolidation (red arrow) with a hugely dilated stomach (black arrow).

### Actual Diagnosis

Because of the high suspicion for H-type tracheoesophageal fistula, a diagnostic bronchoscopy is performed, which revealed an H-type tracheoesophageal fistula (Fig 2).

### The Condition

The H-type fistula is an uncommon type of tracheoesophageal fistula accounting for 4% of cases. The child usually presents with coughing, choking, and cyanosis during feedings. However, the condition is seldom diagnosed in the neonatal period because the symptoms coincide with gastroesophageal reflux and faulty feeding, which are more common. These infants develop recurrent episodes of pneumonia which are also common in gastroesophageal reflux. A dilated stomach on radiography or contrast study tends to give a clue toward H-fistula. Pull-up esophagogram is beneficial, but it is practically difficult to perform in an actively crying child. The close apposition of the trachea to the esophagus and the obliquity of the fistula keeps the fistula occluded for most of the time. The fistula opens when



**Figure 2.** Bronchoscopy showing trachea, with the fistula being cannulated by a guidewire.

the esophagus moves up during swallowing, allowing esophageal content to enter the trachea. Hence, the esophagogram is not a very sensitive investigation and often misses the fistula (50% cases). Bronchoscopy is the diagnostic procedure of choice, which gives a magnified vision and allows cannulation of the fistula. This helps in easy identification of the fistula during surgical exploration.

### Management

Surgical repair is the treatment of choice. The fistula can be approached through the right-sided low cervical incision. Rarely, a right thoracotomy is required in cases of thoracic level fistula. Operative complications include tracheal edema, damage to the recurrent laryngeal nerve, esophageal leak, and recurrence.

### Patient Course

The infant underwent an open repair of the tracheoesophageal fistula. The postoperative period was uneventful. He was thriving and had no issues at the 6-month postoperative follow-up.

### Lessons for the Clinician

- H-type tracheoesophageal fistula is a life-threatening disease that can present without the classic cough or choking while feeding.
- A high index of suspicion is needed to diagnose and treat H-fistula to prevent dangerous complications.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathophysiology of air leaks
- Recognize the clinical, laboratory, and imaging features of air leaks
- Recognize the clinical features of extrapulmonary causes of respiratory distress
- Recognize the imaging features of extrapulmonary causes of respiratory distress

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress

## Suggested Reading

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# Index of Suspicion in the Nursery

## 3 Abdominal Distention and Bloody Stools in a 2-week-old Term Neonate

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### PRESENTATION

A 2-week-old female neonate is born via cesarean section at 39 2/7 weeks to a 34-year-old gravida 3, para 2 woman with adequate prenatal care and negative serologic findings. During pregnancy, the mother develops gestational diabetes that was both diet and insulin controlled. The infant is exclusively breastfeeding at home.

At 17 days of age, the infant is brought to the emergency department (ED) with acute onset of bloody stools that occurred once, along with lime-yellow vomitus concerning for bilious emesis. The mother reports that the infant had been fussy the previous day with increased vomiting and nasal mucous discharge requiring bulb suction. She calls the pediatrician who recommends obtaining a rectal temperature, which is 98.6°F (37°C). Two hours later, the infant develops the rectal bleeding episode (Fig 1) and is brought to the ED at our institution.

In the ED, the physical examination findings are significant for increased fussiness on abdominal palpation, moderately distended firm abdomen, increased tympany, absence of bowel sounds, bright red blood in the diaper, and no anal fissures. Admission vital signs include a temperature of 99.3°F (37.4°C), heart rate of 152 beats/min, respiratory rate of 48 breaths/min, and oxygen saturation of 100% in room air. Complete blood cell count in the ED shows no evidence of leukocytosis, bandemia, or eosinophilia (white blood cell count of  $16,000/\mu\text{L}$  [ $16 \times 10^9/\text{L}$ ] with 1 band, platelets of  $477 \times 10^3/\mu\text{L}$  [ $477 \times 10^9/\text{L}$ ]). Coagulation profile is within normal limits (prothrombin time 12.6 seconds, partial thromboplastin time 28 seconds, international normalized ratio 1.0). Abdominal radiography in the ED shows “abnormal dilated bowel, without free air or pneumatosis. Ileus, necrotizing enterocolitis (NEC), and enteritis should be considered. The appearance is less consistent with malrotation; however, upper gastrointestinal (GI) endoscopy is recommended as clinically indicated” (Fig 2). Upper GI endoscopy is performed, which reveals no evidence of malrotation with persistent dilated distal bowel (Fig 3).

The infant is admitted to the pediatrics department and a surgery consultation is requested. Abdominal ultrasonography (AUS) reveals no evidence of pneumatosis with dilated bowel loops filled with liquid stools and moderate to large ascites with low-level internal echoes (Fig 4). The patient is given nothing by mouth, with a Replogle tube used for low intermittent suction and the infant is started on intravenous fluids. Being concerned about this unusual presentation in a term neonate, the NICU team decides to transfer her to their service. A sepsis evaluation is conducted and stool cultures are sent for bacterial as well as viral infections. Full AUS is performed to rule out ovarian cyst or ruptured ureterocele.

**AUTHOR DISCLOSURE** Ms McClelland and Dr Ibrahim have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Bright red blood in the diaper of the patient.

The AUS reveals normal liver, kidneys, and ovaries. Follow-up abdominal radiography shows persistent dilated bowel loops with no transition point. A barium enema is ordered after clearing of the upper GI contrast and shows normal colon with possible small bowel obstruction in the jejunum or ileum, which was ruled out on further abdominal radiography (Fig 5). On further clarification, the mother reports that the sibling was sick 2 weeks ago with upper respiratory tract symptoms. A respiratory viral panel is sent and is positive for rhino/enterovirus infection.

## DISCUSSION

Hematochezia is the passage of gross blood per rectum. Factors necessary in assessing a child with hematochezia include age of the patient, color of the blood, presence of

abdominal pain/tenderness, and history of altered bowel movements. In 10% to 15% of mucosal or variceal hemorrhages from the upper GI tract, presentation can be melena without hematochezia. (1) Melena or dark blood usually originates from the stomach, duodenum, small bowel, or colon proximal to the ligament of Treitz.

Hematochezia in a neonate can occur because of various causes, ranging from benign to life-threatening conditions. Examples of benign etiologies include swallowed maternal blood (during delivery or nipple cracks during nursing), anal fissures, and milk protein allergy. Examples of more serious conditions include bacterial or viral infections (herpes simplex virus, adenovirus) causing colitis, NEC, or GI malformations. (2)

Causes can be divided into different categories: 1) allergy (eg, milk protein); 2) intolerance; 3) exogenous source such as swallowed maternal blood; 4) gastrointestinal such as anal fissures, Hirschsprung disease with enterocolitis, malrotation with volvulus, intussusception, Meckel diverticulum; 5) vascular malformations (hemangioma, arteriovenous); 6) infections, either bacterial (group B *Streptococcus*, *Escherichia coli*) or viral (herpes virus or cytomegalovirus), and infectious colitis (salmonella, shigella, rotavirus, norovirus); 7) hematologic disorders such as thrombocytopenia, vitamin K deficiency, disseminated intravascular coagulopathy; and 8) hypoperfusion to the gut such as NEC or congenital heart disease. (2)

The clinical presentation of the neonate at the onset of bloody stools helps narrow the differential diagnosis. In an ill-appearing neonate with abdominal distention and tenderness, bowel ischemia, with a manifestation of intussusception,

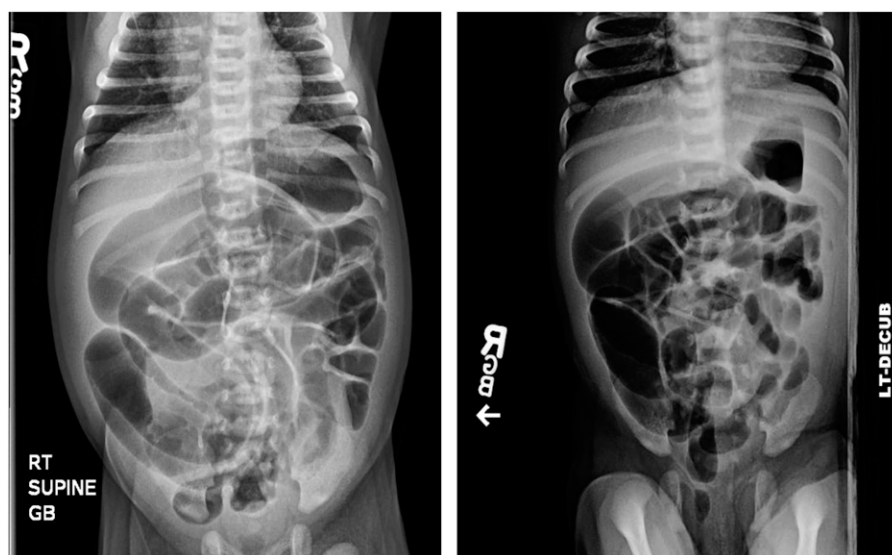


Figure 2. An anteroposterior view and left lateral decubitus of the patient showing abnormal dilated bowel with no free air or pneumatosis.





Figure 3. An upper gastrointestinal series of the patient showing no evidence of malrotation with persistent dilated distal bowel loops.

midgut volvulus, or mesenteric thrombosis, can be the cause. In children younger than 2 years, idiopathic intussusception can present with sudden onset of abdominal pain/tenderness and vomiting, followed by the passage of red currant jelly stools; these signs can be preceded by a viral infection in younger newborns versus a leading point such as Meckel diverticulum or polyp or nodular lymphoid hyperplasia in older children.

Painless hematochezia can be the result of Meckel diverticulum (occurring at <2 years of age in 50% of cases), polyp or intestinal duplication, malformation or superior mesenteric artery aneurysm.

One of the most serious causes of morbidity with bloody stools per rectum in a newborn is NEC, though it is uncommon in term neonates (1 in 20,000). (3) It presents clinically with emesis, abdominal distention, and radiographic findings of pneumatosis intestinalis, portal venous gas, or pneumoperitoneum. An alternative imaging modality that can aid in confirming the diagnosis is ultrasonography. Findings on

ultrasonography include portal venous gas, pneumoperitoneum, increased wall thickness, absent perfusion, or free fluid in the abdomen.

Anal fissures typically present with blood on the outside of normal-appearing stools, with physical examination findings of a fissure in the perianal area, usually posteriorly. Malrotation with midgut volvulus can be responsible for 75% of cases in the first month. Typically, it presents with sudden onset of bilious emesis, increasing abdominal distention, and eventually bowel necrosis leading to shock. Radiographically it can present with a gasless abdomen or distended bowel loops.

Milk protein enterocolitis is another entity that can present early but typically between 1 month and 1 year of age.

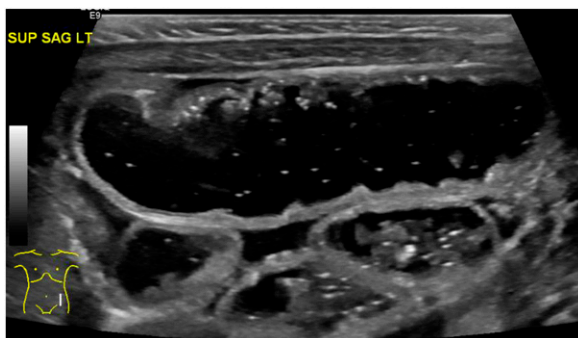


Figure 4. Dilated bowel loops with liquid stools on abdominal ultrasonography.



Figure 5. Barium enema showing normal colon.

About half of the patients are younger than 6 months. Symptoms related to the GI tract such as regurgitation, vomiting, colic, diarrhea, and bloody stools occur in 88.7% of the cases. (4) The most serious form of milk protein allergy in infants is protein-induced enterocolitis syndrome, which can present with vomiting, diarrhea, and a sepsislike picture.

Viral infections such as herpes or cytomegalovirus can lead to infectious colitis. In a rare case of congenital adenovirus infection, a 3-day-old infant presented with hematochezia and thrombocytopenia. (5)

In our case, the patient had a sibling with upper respiratory tract illness 2 weeks earlier. The patient tested positive for rhinovirus/enterovirus infection. The polymerase chain reaction assay in our laboratory cannot differentiate between both infections. We think that the patient might have developed viral colitis, which could have led to intermittent intussusception and presented with bloody stools. Another possibility is a severe form of cow milk protein allergy, but this is less likely given the lack of family history and the fact that the patient was only 2 weeks old.

## FOLLOW-UP

The patient's abdominal symptoms improved, and the episodes of bloody stool ceased after 2 days of bowel rest. On consultation, the GI service recommended starting the patient on a special hypoallergenic infant formula to rule out severe milk protein allergy. The infant was discharged from the hospital after 5 days on full feeds with follow-up appointments scheduled with the pediatrician and the GI service.

## Lessons for the Clinician

- Differential diagnosis of acute abdominal distention and bloody stools in a term neonate can be necrotizing enterocolitis, malrotation, or acute intestinal obstruction in an infant.
- However, despite being uncommon, severe milk protein allergy or a viral infection leading to colitis and/or intermittent intussusception can have a similar presentation.

- Acute abdominal distention and bright rectal bleeding can also occur because of a medical cause in some cases and might not need surgical intervention.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the laboratory and radiographic findings, evaluation, and management of GI bleeding in newborn infants
- Recognize the clinical signs, imaging features, and treatment of neonatal intussusception
- Know the clinical and diagnostic features, evaluation, management, and complications of NEC
- Know the differential diagnosis, diagnostic and laboratory features, and approach to management of infectious enteritis and colitis in the neonate
- Know the clinical manifestations, diagnosis, and management of allergic enteritis and colitis such as milk protein allergy
- Know the clinical manifestations and differential diagnosis of GI bleeding in newborn infants, including the various coagulation disorders that cause GI hemorrhage

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Katybeth McClelland and John Ibrahim

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## Velamentous Cord Insertion

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wavelike undulating pattern, with waves having regular frequency and amplitude

**AUTHOR DISCLOSURES** Drs Weyenberg and Neerhof have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. Arterial Umbilical Cord Gas Values

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles/min, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)

- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
  - Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period.
  - Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent.

### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wavelike undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes.

### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes.
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent



- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

- Bradycardia not accompanied by absent variability
- Tachycardia
- Minimal or marked baseline variability
- Absent variability without recurrent decelerations
- Absence of induced accelerations after fetal stimulation
- Recurrent variable decelerations with minimal or moderate variability
- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

- Absent variability with any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## CASE PRESENTATION

### History

A 35-year-old gravida 1 para 0 woman presents for management of newly diagnosed gestational diabetes mellitus. She is at 24 weeks, 6 days of gestation based on her last menstrual period and consistent with 5-week ultrasonography findings. She did not have a diagnosis of diabetes before this presentation. Her serum glucose concentration was 555 mg/dL (30.8 mmol/L) 1 hour after having an oral 50-g glucose drink. She reported a 2- to 3-week history of polydipsia and urinary frequency.

Her medical history is significant for fatty liver, obesity, mild asthma, gastroesophageal reflux, and a bicornuate uterus. Her surgical history is notable for a loop electrosurgical excision procedure of her cervix. She has smoked a half pack of cigarettes per day for 6 years. She denies alcohol or illicit drug use. She is taking a prenatal vitamin and no other medication.

On admission, she is well appearing and in no acute distress. Her blood pressure is 144/80 mm Hg, pulse 98 beats/min, and oxygen saturation 98%. Her physical examination findings are unremarkable. Laboratory evaluation is significant for a fasting blood glucose of 346 mg/dL (19.2 mmol/L) and a hemoglobin A1c of 10.7%. Her potassium is 4.4 mEq/L (4 mmol/L), bicarbonate level is 20 mEq/L (20 mmol/L; reference range 22–29 mEq/L [22–20 mmol/L]), anion gap is 21 mEq/L (21 mmol/L; reference range 20–26 mEq/L [20–26 mmol/L]), and creatinine is 0.7 mg/dL (53.4  $\mu$ mol/L). Her serum  $\beta$ -hydroxybutyrate is 2.5 mmol/L (reference range 0–0.3 mmol/L) and her arterial pH is 7.43. Her 24-hour urine protein is 230 mg (reference range, 0–300 mg).

Level II anatomy ultrasonography previously performed at 20 weeks and 4 days of gestation demonstrated normal growth and anatomy, and normal amniotic fluid volume. The placenta was anterior right lateral and the placental cord insertion was challenging to optimally visualize, but appeared normal. A uterine synechia was visualized in the right lower quadrant.

The FHR tracing is demonstrated in Fig 1.

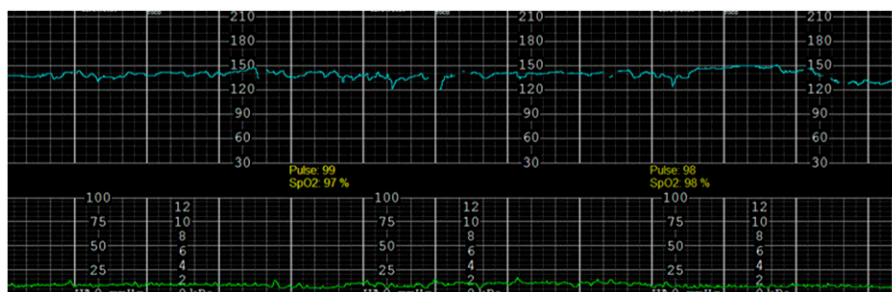


Figure 1. Electronic fetal monitoring strip 1.

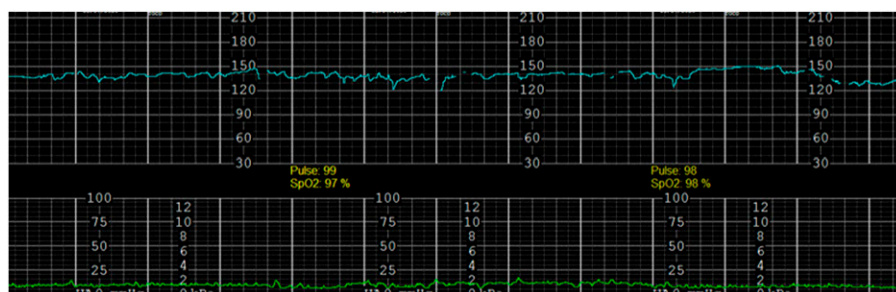


Figure 1. Electronic fetal monitoring strip 1.

Findings from EFM strip 1 are as follows:

- Variability: Moderate
- Baseline rate: 135 beats/min
- Accelerations: 10×10
- Decelerations: None
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category I, normal tracing, predictive of normal acid-base status
- Action: Continue FHR monitoring

diagnosed with gestational diabetes and gestational hypertension. Pregestational diabetes was strongly suspected because of the extreme elevation of her blood glucose. Endocrinology was consulted and an intravenous infusion of insulin was started. During her initial evaluation and initiation of management, the FHR tracing became significant for spontaneous prolonged deceleration to 60 beats/min for a period of 2 to 6 minutes (Fig 2). These episodes resolved with maternal repositioning and maternal oxygen administration. Following the deceleration, there were periods of minimal variability and fetal tachycardia (Fig 3). The decelerations were not associated with contractions.

## CASE PROGRESSION

As a result of the laboratory abnormalities reported earlier and mild range elevation in blood pressure, the patient was

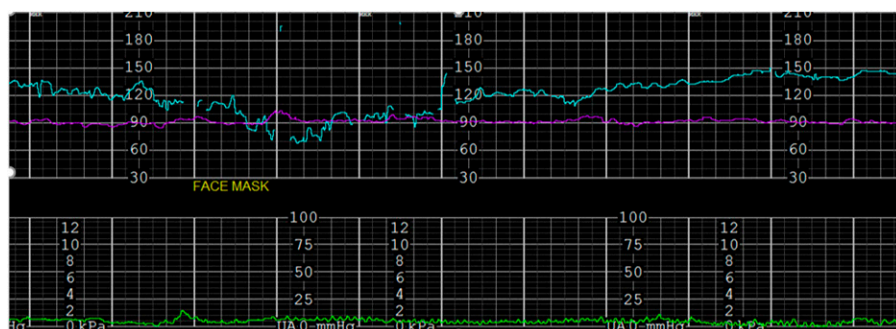


Figure 2. Electronic fetal monitoring strip 2.

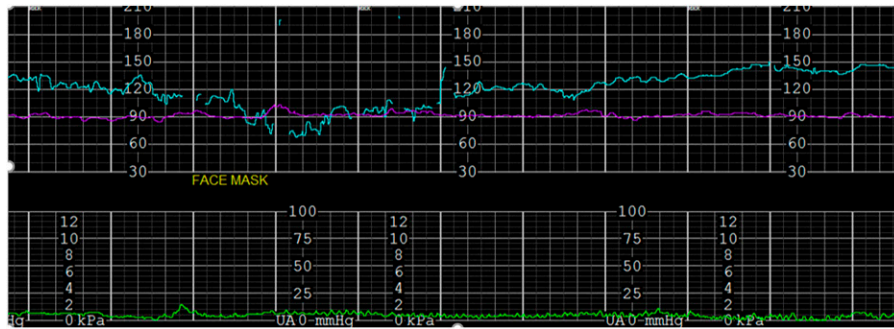


Figure 2. Electronic fetal monitoring strip 2.

Findings from EFM strip 2 are as follows:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Accelerations: Present
- Decelerations: Prolonged deceleration to nadir of 70 beats/min for 3 minutes
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Transient compression of umbilical cord, fetal acidosis because of maternal diabetic ketoacidosis, placental insufficiency, and velamentous cord insertion
- Action: The patient was repositioned and maternal oxygen administered, and overall fetal status returned to reassuring with moderate variability

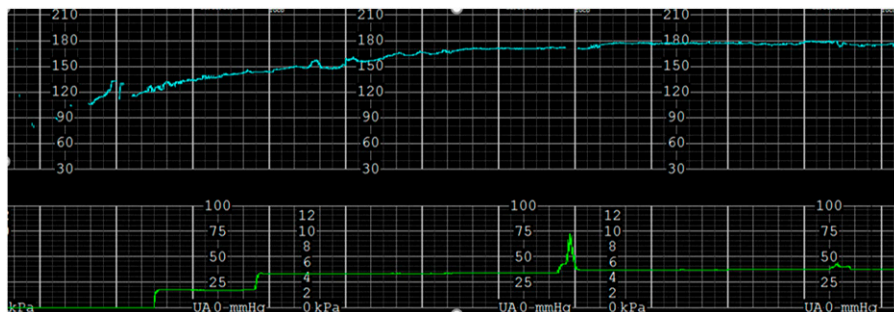


Figure 3. Electronic fetal monitoring strip 3.

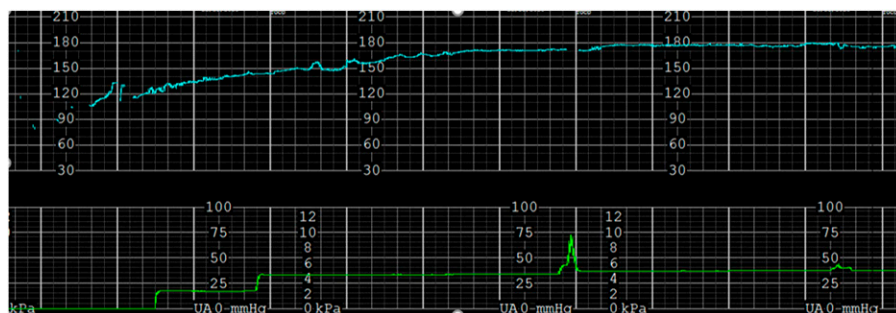


Figure 3. Electronic fetal monitoring strip 3.

Findings from EFM strip 3 are as follows:

- Variability: Minimal
- Baseline rate: 170 beats/min
- Accelerations: None
- Decelerations: Prolonged deceleration to 90 beats/min for 8 minutes audible immediately before the tracing shown in Fig 3
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Transient compression of umbilical cord, fetal acidosis because of maternal diabetic ketoacidosis, placental insufficiency, and velamentous cord insertion

- Action: The patient was repositioned and maternal oxygen administered, and overall fetal status returned to reassuring with moderate variability

Because of the severity and length of the FHR decelerations, it was decided to proceed with betamethasone administration for fetal lung maturity and 12 hours of intravenous magnesium sulfate for neuroprotection. She received 12.5 mg of betamethasone via intramuscular injection and a 6-g bolus of intravenous magnesium followed by a 2 g/hour infusion of magnesium over 12 hours. Her blood glucose levels ranged from 243 to 325 mg/dL (13.4–18 mmol/L) overnight. Bedside glucose assessment was performed every 2 hours. Serial laboratory evaluation overnight was significant for resolution of the anion gap and normalization of the serum  $\beta$ -hydroxybutyrate. Intravenous insulin was discontinued and subcutaneous insulin was initiated. Intermittent prolonged FHR decelerations continued (Fig 4).

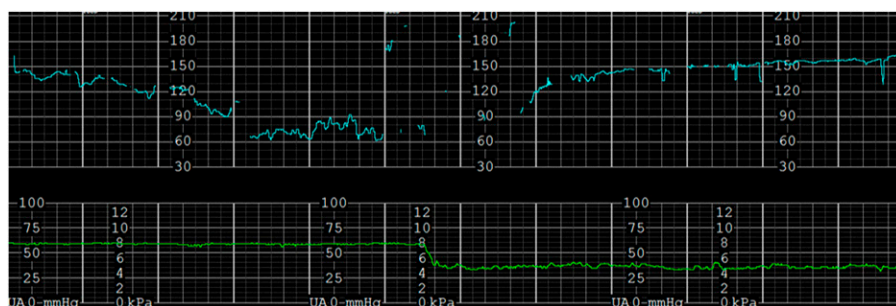


Figure 4. Electronic fetal monitoring strip 4.

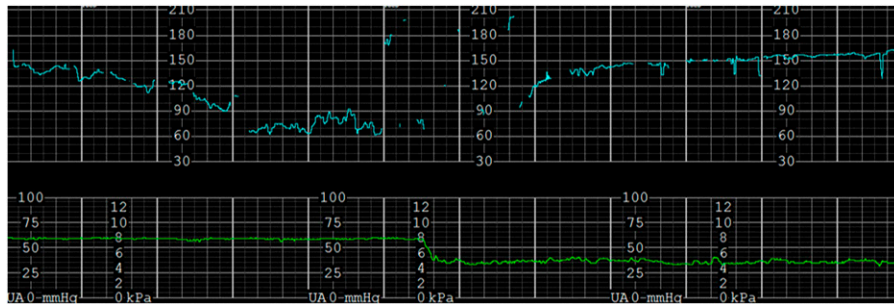


Figure 4. Electronic fetal monitoring strip 4.

Findings from EFM strip 4 are as follows:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Accelerations: None
- Decelerations: Prolonged deceleration to 70 beats/min for 5 minutes
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Transient compression of umbilical cord, velamentous cord insertion, and placental insufficiency
- Action: The patient was repositioned and maternal oxygen administered, and overall fetal status returned to reassuring with moderate variability

Her blood glucose was consistently greater than 300 mg/dL (16.6 mmol/L) on hospital day 2, and therefore intravenous insulin infusion was restarted. Additional prolonged FHR decelerations were noted overnight on hospital day 2, similar to prior episodes. All episodes resolved with maternal repositioning and maternal oxygen administration. These FHR decelerations continued to occur intermittently between hospital days 3 and 5. The intravenous insulin rate was decreased gradually and discontinued on

hospital day 5. Fetal assessment ultrasonography performed on hospital day 4 at 25 weeks and 2 days of gestation was significant for an estimated fetal weight of 831 g (50th percentile); the placental location was anterior and the amniotic fluid volume was normal. The placental cord insertion was again thought to be normal. Fetal monitoring was transitioned to nonstress testing 3 times daily with continued occasional prolonged decelerations noted between hospital days 6 and 10. The patient was discharged on hospital day 10 with nonstress tests performed 3 times per week and an insulin regimen. The patient followed up in the clinic 2 and 4 days after discharge.

During her appointment 4 days after discharge at a gestational age of 26 weeks and 5 days, she reported a severe headache and vision changes and her blood pressure was 130/76 mm Hg. She was readmitted for an evaluation of preeclampsia. Her headache and blurry vision resolved after oral butalbital/acetaminophen/caffeine administration. A 24-hour urine protein yielded 320 mg of protein and she was diagnosed with preeclampsia without severe features. Her blood pressure remained mostly normotensive with occasional blood pressure readings in the mild range ( $\geq 140/90$ ). Three days after this admission, prolonged FHR decelerations were noted and were increasing in length and frequency. The most severe deceleration lasted for 8 minutes to a nadir of 60 beats/min (Fig 5).

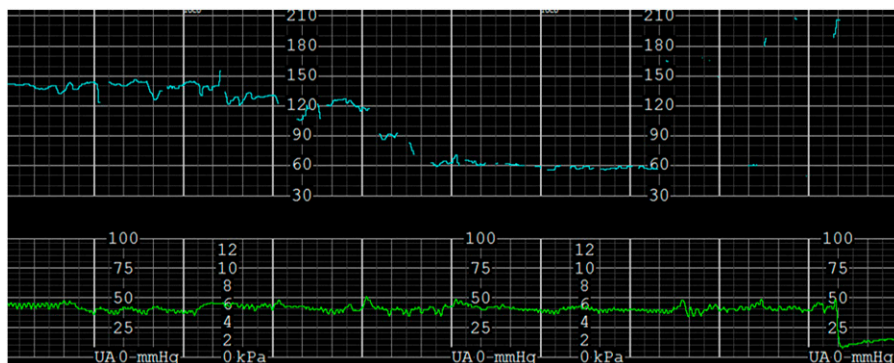


Figure 5. Electronic fetal monitoring strip 5.



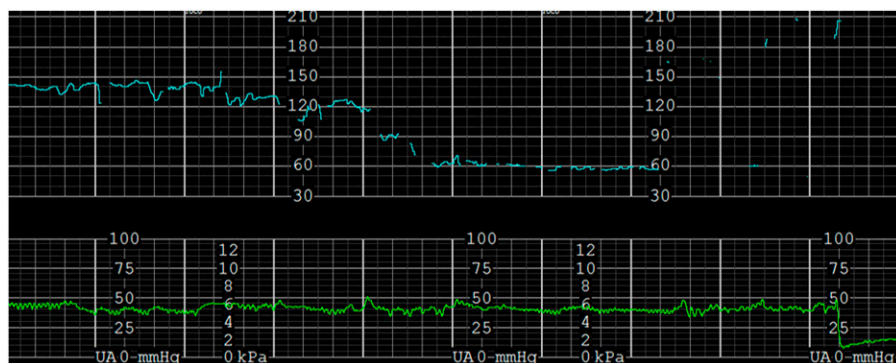


Figure 5. Electronic fetal monitoring strip 5.

Findings from EFM strip 5 are as follows:

- Variability: Moderate
- Baseline rate: 140 beats/min
- Accelerations: None
- Decelerations: Prolonged deceleration to 60 beats/min for 8 minutes
- Episodic pattern: None
- Periodic pattern: None
- Uterine contractions: None
- Interpretation: Category II
- Differential diagnosis: Transient compression of umbilical cord, velamentous cord insertion, and placental insufficiency
- Action: The patient was repositioned and maternal oxygen administered, and overall fetal status returned to reassuring with moderate variability

Because of the continued prolonged decelerations that were generally increasing in length and frequency, it was decided to proceed with delivery. Gestational age at delivery was 27 weeks and 1 day. A primary low-transverse cesarean section was performed. The pediatric team was present at the time of delivery.

## OUTCOME

A liveborn 970-g female infant in breech position was delivered via cesarean section. The infant initially had a weak cry at delivery with an irregular breathing pattern and normal heart rate. After oral suctioning, the infant was placed on continuous positive airway pressure. The infant's Apgar scores were 6, 8, and 9 at 1, 5, and 10 minutes, respectively. The infant was transferred to the infant special care unit because of prematurity. She underwent extubation on day 8 after birth and was slowly weaned to room air. Her head ultrasonography and retinal examination findings were unremarkable.

Intraoperative findings were significant for velamentous placental cord insertion traversing a 5.5-cm portion of membranes. No abruption was noted. The mother recovered from the cesarean section without complications. Her blood pressure was well-controlled. She continues to require insulin to manage her blood glucose and now carries the diagnosis of type 2 diabetes mellitus.

## DISCUSSION

The majority of umbilical cords insert into the placenta in a central location. This allows protection of the umbilical cord vessels by Wharton jelly. In approximately 6.3% of singleton gestations, the umbilical cord inserts at the placental edge and is referred to as a "marginal cord insertion." In approximately 1.5% of placentas, the umbilical cord traverses the membranes before inserting into the edge of the placenta and is referred to as a "velamentous cord insertion" (VCI). (1) In the case of a VCI, the umbilical vessels are not protected by Wharton jelly and are therefore more susceptible to physical compression or injury. Compression of the umbilical vein may cause a decrease in preload, which frequently results in a compensatory tachycardia. Compression of the umbilical arteries causes an increase in fetal afterload. This leads to stimulation of fetal baroreceptors, resulting in a vagal reflex and consequently, bradycardia. (2) The fetal bradycardia manifests as variable and/or prolonged FHR decelerations on monitoring. More severe compression of the fetal vessels may lead to total occlusion, and possibly fetal death. The mechanism of compression of fetal umbilical vessels is fetal movement and is therefore independent of uterine contractions. (3)(4)

Anomalous cord insertion locations are more common in multiple gestations and with assisted reproductive technology. (5) VCI may be challenging to confirm on



ultrasonography, depending on the location of the cord insertion and maternal habitus. In most cases, VCI is an incidental finding. However, VCI is associated with an increased risk of compression of the umbilical vessels. This can result in FHR abnormalities, especially during labor, in cases where the VCI is in the lower uterus. VCI is also associated with an increased risk of fetal death as a result of vascular compression. VCI may also be associated with an increased risk of fetal growth restriction, preterm labor, placental abruption, and neonatal death. (3)(6) Because of these risks, it is recommended to monitor pregnancies with anomalous cord insertion with antenatal FHR testing and serial fetal ultrasonography assessment. (7)

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor including reassuring and nonreassuring and indeterminate patterns

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## Strip of the Month: Velamentous Cord Insertion

Lydia Weyenberg and Mark G. Neerhof

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## Head Compression, Ischemic Encephalopathy, and Adverse Outcome

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A 2,722-g male infant is born at 37 6/7 weeks' gestation via cesarean delivery to a 26-year-old gravida 4, para 3 woman who is group B *Streptococcus* negative and had an unremarkable prenatal course. She presented to the labor and delivery department when she developed spontaneous contractions. Hospital policy required that all potential deliveries before 39 weeks' gestation be evaluated by a perinatologist. As part of the evaluation, the perinatologist performed fetal ultrasonography and found that the biophysical profile score was 8/8 with 2 points each for breathing, movement, tone, and amniotic fluid index. The fetal tracing was interpreted as nonreassuring and category II. At that time, the cervix was minimally effaced and only dilated to 2 cm. The perinatologist approved of the plan to allow labor to continue because the gestation was at term.

Contractions continued over the next 24 hours without cervical change. Because of this failure to make progress, the obstetrician started oxytocin; however, within 1 hour of administration, the fetal tracing worsened. *Plaintiff experts said that these findings suggested excessive uterine activity, including increased uterine tone and coupled contractions. They stated that these effects of oxytocin did not allow the fetus to have an adequate rest period for recovery. The obstetrician retained by the defense acknowledged that the fetal monitor strips had these findings, but said that because tachysystole was not occurring by the strict definition (>5 contractions in a 10-minute period averaged over 30 minutes), the fetus was not in danger. The plaintiff obstetric expert pointed out that the guidelines accompanying the promulgation of the "tachysystole standard" was far less meaningful in terms of potential damage to the fetus than the lack of rest time, tone, and duration of contractions, which are important but provide no numerical guidelines. The plaintiff obstetrician explained that the:*

- 1) normal range of contraction frequency is 2 to 4.5 over 10 minutes and a frequency beyond that is excessive*
- 2) normal range of contraction intensity (amplitude) is 25 to 75 mm Hg and excessive is not defined*
- 3) normal contraction duration is 60 to 90 seconds and a duration greater than 90 seconds is excessive*
- 4) normal resting tone (intrauterine pressure catheter) is 15 to 20 mm Hg and a tone greater than 25 mm Hg is excessive*
- 5) normal interval (peak of one contraction to the peak of the next) is greater than 2 to 4 minutes and an interval greater than 2 minutes is excessive*
- 6) normal range from the end of one contraction to the beginning of the next is 1 to 2 minutes and a range less than 1 minute is excessive*
- 7) normal rest time (the percentage of time that the uterus is at rest [not contracting]) is less than or equal to 50% and a rest time greater than 50% is excessive*

**AUTHOR DISCLOSURE** Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Irrespective of the fetal tracing findings, the oxytocin infusion was maintained and incrementally increased. *The plaintiff obstetrician contended that this conduct was below a reasonable standard of care. He maintained that the likelihood of safe delivery by the vaginal route was very remote given the poor progress in labor despite the excessive uterine activity and the nonreassuring tracings from even before the oxytocin administration. He opined that oxytocin needed to be discontinued and a cesarean delivery was needed. The obstetrician retained by the defense disagreed and pointed out that tachysystole (referring only to the frequency of contractions) was not present and that too many cesarean sections were being performed unnecessarily and that this case is an example of a situation that definitely did not require a cesarean delivery. The defense team further contended that monitoring has never been shown to decrease the incidence of cerebral palsy. The plaintiff expert responded by saying that electronic fetal monitoring has unequivocally reduced the risk of intrapartum stillbirth as well as the risk of adverse outcomes related to hypoxia. There is no reported example of an asphyxiated fetus without an abnormal pattern and no fetus has died unexpectedly while being monitored. There is no plausible justification for applying the fetal monitor and not paying attention to its output.*

The patient's membranes were artificially ruptured 11 hours before delivery, revealing clear fluid. Nine hours before delivery, the obstetrician performed an amnioinfusion in response to a 9-minute deceleration. Nonreassuring patterns persisted and the patient was placed on oxygen, given a bolus of normal saline, and had her position changed, but the tracings remained nonreassuring. *The plaintiff experts maintained that given the diminished prospects of a safe vaginal delivery because the ongoing abnormalities of the tracing were likely to be exacerbated during the second stage of labor, a cesarean section was again required. They noted that the objective of obstetrical care is not to see how close one may get to disaster, but rather to avoid the need for rescue of the compromised fetus. At this time, the plaintiff experts opined that the delivery was likely to result in a stressed fetus that was nevertheless neurologically intact. The neonatologist retained by the plaintiff stated that the newborn would have likely needed some initial stabilization because of the difficult intrapartum course, but that it was more probable than not that the patient would have avoided brain injury.*

As the labor continued, variable and late decelerations developed with increasing frequency but with the persistence of some baseline variability. *The defense argued that the finding of variability was still reassuring because it had not completely disappeared. Plaintiff experts pointed out that variability by itself cannot serve as the only indicator of fetal well-being on the heart rate monitor. They noted that variability is*

*controlled in the deeper centers of the fetal brain, which preferentially receive oxygen and blood flow (from the vertebral basilar system) over the higher cortical levels (which are perfused by the cerebral arteries) and preferentially over other systemic organs as well. They stated that adequate perfusion of the part of the brain that controls heart rate variability does not mean that there is enough oxygen or blood flow available to also adequately perfuse the rest of the brain, including areas that would otherwise develop to mediate motor function and normal cognitive function. The plaintiff experts opined that variability of the fetal heart rate may remain present on the tracing, because this is controlled by the brain stem, even though there may be hypoxic-ischemic injury to the rest of the brain. They opined that too many uterine contractions over too short a period in labor caused a lack of blood flow (ischemia) and a lack of oxygen. During labor, especially after rupture of the membranes, the plaintiffs reported that the fetal head was repeatedly subjected to mechanical forces during the very prolonged, nonprogressive labor, being pushed against the unyielding cervix, with excessive oxytocin-induced contractions.*

After 16 hours of oxytocin administration and 9 hours of failed progress in labor, the obstetrician decided to perform a cesarean delivery. The umbilical venous gas had a pH of 7.32, a  $\text{PCO}_2$  of 43 mm Hg (5.7 kPa), a  $\text{PO}_2$  of 20 mm Hg (2.6 kPa), and a base excess of  $-4$ ; the other gas was not labeled and had a pH of 7.31, a  $\text{PCO}_2$  of 47 mm Hg (6.2 kPa), a  $\text{PO}_2$  of 15 mm Hg (2 kPa), and a base excess of  $-2.4$ . *The plaintiff experts pointed out that both of these gases were likely from the same vessel, and most likely the umbilical vein. They stated that the average pH difference between cord arterial and venous samples is expected to be 0.04 to 0.10, which did not occur in this scenario, suggesting that the samples were from the same vessel.*

After delivery, the infant briefly required positive pressure ventilation. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively, and the infant was transferred to the nursery where a physical examination revealed that the infant was appropriate for gestational age, with a birthweight of 2.7 kg, a length of 49.5 cm, and a head circumference of 33 cm. No dysmorphic features were noted. His anterior fontanel was soft and flat and his tone was normal, but he was lethargic, tachypneic with shallow respirations, and had no cry. Capillary blood saturation was 77% in room air. Two hours after birth, he was transferred to the NICU. On arrival at the unit, his blood pressure (BP) and perfusion were normal. His complete blood cell count and electrolytes were normal; a blood culture specimen was drawn which subsequently yielded *Staphylococcus hominis*, which the team at the birth hospital dismissed as a contaminant. A capillary blood gas at 2½ hours after birth showed a pH of

7.27, a  $P_{CO_2}$  of 45 mm Hg (5.9 kPa), a  $P_{O_2}$  of 72 mm Hg (9.5 kPa), and a base deficit of  $-6.7$ . The infant was treated with ampicillin and gentamicin and placed in a high-flow nasal cannula with a fraction of inspired oxygen of 0.4. Five hours after birth, he developed seizures manifested by apnea, color change, increased tone, and sucking of his lips; the team treated him with phenobarbital. The infant's apnea became so severe that he required intubation. At 9 hours of age, his fontanel was full. A cranial ultrasonography scan was normal. Because of the unremitting seizures, he was transferred to a hospital with a higher level of care.

At 11 hours of age, the infant arrived at the referral center and the team started acyclovir and obtained a computed tomography (CT) scan. The CT scan showed herniation of brain tissue at the level of the foramen magnum and an acute diffuse global ischemic infarction involving almost all of the cerebral hemispheres, cerebellum, basal ganglia, and portions of the thalamus. There was a mass effect on the lateral ventricles, which were displaced toward midline as well as complete compression of the third and fourth ventricles. The ammonia level was marginally high, and liver enzymes and creatinine levels were within normal limits. The team concluded that the infant had suffered head trauma and that he would benefit from intracranial pressure (ICP) monitoring at a hospital with a higher level of care.

Twenty-four hours after birth, the infant arrived at the third medical center. Upon arrival, he was found to have a bulging fontanel, a head circumference that had increased by 1.5 cm, and a decreasing BP for which he received normal saline boluses and inotropic support. His pupils were slow to react, he did not withdraw from painful stimuli, and he showed no spontaneous body movements. A repeat complete blood cell count was normal; his serum sodium was 122 mEq/L (122 mmol/L), and he had evidence of bleeding after blood draws. He developed disseminated intravascular coagulopathy with an elevated prothrombin time, partial thromboplastin time, and D-dimer concentration. An assessment for an inherited clotting disorder, including abnormalities in factor V Leiden, protein C, homocysteine, protein S, and lupus anticoagulation as well as a mutation in prothrombin gene, revealed no abnormality. Magnetic resonance imaging was performed when the infant was 5 days of age, which confirmed a diffuse ischemic injury involving nearly the entire supratentorial parenchyma.

The infant underwent extubation at 6 days of age. He was discharged at 5 weeks of age with a gastrostomy and antiseizure medications. *The plaintiff neonatologist and neurologist maintained emphatically that head trauma with cerebral ischemia during the intrapartum period was the etiology of*

*the infant's brain damage. They stated that uterine forces compressed the fetal brain sufficiently to result in intermittent ischemia and hypoxia as evidenced by the decelerations in the fetal heart rate and mechanical trauma to the brain led to the herniation. The defense experts contended that the cause was an unknown viral infection, or genetic or metabolic disorder that was yet to be determined and that the damage had occurred before the mother was admitted to the hospital. Furthermore, the defense maintained that the fetus was not low enough in the pelvis to have his head traumatized by a bony pelvis nor was there an instrumental delivery by forceps or a vacuum extractor.*

*The plaintiff experts maintained that during the long, non-productive labor, the prolonged contractions, along with the ruptured membranes, compressed the fetal head against a hard cervix for a prolonged time. Forceful uterine contractions for hours with a cervical dilation of 2 to 3 cm provided a rigid obstruction that was not overcome. The plaintiff pointed out that usually a fetus makes serial adjustments and wiggles and squirms its way through the birth canal with some head molding. However, if the infant is not fitting properly in the pelvis then it is similar to trying to fit a piano through a door.*

*The defense argued that the infant did not have cardiovascular issues after birth and the liver function tests and creatinine were evidence that there was no acute systemic hypoxia. The defense's major argument was that it was impossible to have an ischemic insult to the brain during the intrapartum period because the cord pH and Apgar scores were normal. The plaintiff pointed out that global, systemic hypoxia was neither the problem in this fetus nor the proposed mechanism of injury. Instead, they stated that this infant's outcome resulted from head trauma that was sufficient to cause herniation of the brain stem and profound ischemic changes. Furthermore, with head trauma, the cord pH and Apgar scores can be acceptable because cerebral vascular perfusion is impaired not the cardiovascular function. The plaintiff experts opined that this case was not a classic hypoxic-ischemic insult with systemic asphyxia and cardiac failure resulting in diminished cerebral blood flow (CBF; ischemia) but instead, this case involved head trauma. Moreover, one cannot accept the cord pH in this case because of the lack of relationship between the 2 samples and the unlabeled sample.*

*Plaintiff experts pointed out that the "essential criteria" for linking intrapartum events to the timing of an injury and to the long-term outcome are based on a model of injury involving severe asphyxia with metabolic acidemia leading to heart failure and diminished CBF (ischemia). In this case, the plaintiffs noted that the infant's brain ischemia was caused by the excessive pressure exerted to the fetal skull. They stated that in reality, the diagnosis of head trauma derives from the neuroradiologic findings that clinically support the events of labor. They*



*commented that it is important to emphasize that the neuro-radiologic diagnosis of hypoxic-ischemic encephalopathy is made without knowledge of the pH and base deficit of the umbilical cord. The plaintiffs stated that the notion that the link between intrapartum events and adverse neonatal outcome must involve a depressed infant with poor tone, decreased reflexes, a reduced level of consciousness, and an inability to maintain respirations along with arterial cord acidemia and subsequent multiorgan dysfunction, is not valid.*

On follow-up examination, the infant was found to have spastic quadriplegia, global delays, seizure disorder, intellectual disability, microcephaly, scoliosis, and constipation. The case settled without going to trial.

## DISCUSSION

Mechanical events affecting fetal CBF during labor and delivery need to be considered as an explanation for adverse neonatal outcomes, especially when there are significant changes in the previously normal fetal heart rate pattern and the umbilical pH is in the normal range. A neonate who has incurred systemic intrapartum hypoxia often will present with umbilical acidemia and varying degrees of depression ranging from hypotonia and irregular respirations to requiring a full resuscitation. Infants with neurologic injuries related to localized (regional) cerebral ischemia during labor and delivery, on the other hand, present without significant umbilical acidemia and may not be immediately symptomatic. These infants may present hours or days after delivery as the cytotoxic edema builds and the ICP increases and they eventually become symptomatic with apnea, desaturations, and/or seizures or even with more subtle signs.

Physiologically, uterine contractions cause an increase in fetal ICP with the potential to diminish cerebral perfusion. Most often, the fetus easily maintains cerebral perfusion by increasing its BP during a contraction. The fetus further defends its brain against the increases in ICP generated by uterine contractions (especially in combination with maternal pushing) by cerebrovascular autoregulation (physiological mechanism of maintaining CBF during changes in BP) and by increasing further the mean arterial pressure through the Cushing response (increased BP in response to an increased ICP). Because normal arterial BP in the newborn is relatively low, cerebral perfusion pressure already may be dangerously close to the downslope of the autoregulation curve. When uterine contractions come too closely together, are too intense, or the baseline uterine tone is high, the time for the cerebral circulation to recover or “catch up” on oxygenated blood can be insufficient, which can lead to cerebral ischemia. Understanding the formula

that cerebral perfusion pressure is equal to the mean arterial BP minus the ICP underscores the vulnerability of the CBF.

Ischemic injury may occur when the fetus is no longer able to compensate for the forces that are diminishing the cerebral perfusion. Because the affected newborn may not be significantly depressed at birth, these infants will often be transferred to the nursery or room in with the mother, only to deteriorate hours to days later when the cerebral edema builds up to the point of symptoms. Without a full understanding of the course of labor and the fetal responses, the neonatologist might be baffled in terms of understanding the cause of a newborn who develops symptoms including encephalopathy, but had normal cord blood gases and was not depressed immediately after birth. It is important, therefore, under these circumstances, to assess the obstetrical record for the presence of various mechanical risk factors for fetal neurologic injury, including prolonged labor, excessive uterine activity, fetal malposition (especially occiput posterior), and operative vaginal delivery (vacuum or forceps).

Adding to the challenge is the lengthy duration of ruptured membranes because the amniotic fluid is no longer available to buffer the pressure of the uterine contractions. Normal Apgar scores and reasonable cord gases should not be reassuring to the neonatologist in determining the degree of observation and monitoring that a newborn needs if the intrapartum period has red flags, as the intrapartum course in the current case signaled.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the incidence, causes, and pathophysiology, including cellular abnormalities, of acute perinatal asphyxia.

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## ANSWER KEY FOR JULY 2019 NEOREVIEWS

**Impact of Nonmedical Factors on Neurobehavior and Language Outcomes of Preterm Infants:** 1. B; 2. A; 3. D; 4. C; 5. B.  
**NICU Diet, Physical Growth and Nutrient Accretion, and Preterm Infant Brain Development:** 1. D; 2. A; 3. A; 4. D; 5. B.

## Legal Briefs: Head Compression, Ischemic Encephalopathy, and Adverse Outcome

Maureen E. Sims

*NeoReviews* 2019;20:e432

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## A Term Infant with Respiratory Distress at Birth

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### THE CASE

A full-term infant with a prenatal diagnosis of heterotaxy presents with respiratory distress and hypoxia with a postnatal diagnostic radiograph revealing a significant differential in lung expansion.

### PRENATAL AND BIRTH HISTORIES

- Born to a 27-year-old gravida 5, para 4 woman who presented in labor.
- Estimated gestational age: 38 weeks based on last menstrual period.
- Prenatal diagnosis of heterotaxy, with absent right eye, and concern for esophageal atresia or tracheoesophageal fistula because of absent stomach bubble on ultrasonography. Fetal echocardiography was performed, which showed levocardia, an interrupted inferior vena cava with a large azygous continuation to the superior vena cava.
- Prenatal maternal laboratory findings: Blood type B positive, Coombs negative; rubella immune; group B *Streptococcus*–unknown; hepatitis B surface antigen–negative; HIV–negative; syphilis treponemal screening test–negative.
- Delivery: The infant was born via vaginal delivery in vertex position. Apgar scores were 4, 5, and 7 at 1, 5, and 10 minutes, respectively. She had a weak cry and poor tone at delivery. Continuous positive airway pressure of 5 cm H<sub>2</sub>O was initiated. Fraction of inspired oxygen (Fio<sub>2</sub>) was slowly increased to 100% over the next 3 minutes after birth to maintain adequate oxygen saturation. At 7 minutes, the infant was noted to have poor respiratory effort and positive pressure ventilation was initiated. At 10 minutes after birth, she continued to have intermittent apnea and persistent hypoxia, leading to endotracheal intubation with minimal subsequent improvement of oxygen saturation. She was transported to the NICU without difficulty.

### PRESENTATION

#### Progression (Day 1)

- Heart rate: 160 beats/min
- Respiratory rate: 46 breaths/min
- Blood pressure: 79/67 mm Hg
- Oxygen saturation: 90% on 100% Fio<sub>2</sub> delivered via mechanical ventilation
- Temperature: 97.0°F (36.1°C)

#### Physical Examination (Day 1)

- Measurements: Weight 3,690 g (84th percentile), length 47 cm (17th percentile), head circumference 32.5 cm (14th percentile).

**AUTHOR DISCLOSURE** Drs Vachharajani and Herco have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

- General: Female infant in open warmer, orally intubated, and receiving mechanical ventilation.
- Skin: No icterus, no lesions.
- Head: Molding present, anterior and posterior fontanelles soft and flat with aligned sutures. Right eye absent. Left pupil equal, round, and reactive to light. Ears normal position. No preauricular pits or tags. Nares patent. Mucous membranes pink and moist. Central cleft palate. Neck supple with no masses.
- Chest: Bilateral breath sounds equal and clear with good air exchange. Symmetric chest wall movement.
- Cardiovascular: Regular rate and rhythm, no murmurs. The heart sounds were heard in normal location. The apex beat was not felt but the apex impulse was seen on the left side in the fifth intercostal space in the midclavicular line. Brachial and femoral pulses 2+ and symmetric. Capillary refill 2 to 3 seconds.
- Abdomen: Soft and nondistended. No abdominal wall erythema, prominent veins, or visible peristalsis. No hepatosplenomegaly, liver not palpable.
- Genitalia: Normal term female genitalia; patent anus.
- Musculoskeletal: Spine midline and intact. No sacral dimple, hips stable bilaterally.
- Neurologic: Tone appropriate for gestational age.

#### Laboratory Studies (Day 1)

- Arterial blood gas: pH 7.32,  $PCO_2$  46 mm Hg (6.1 kPa),  $PAO_2$  80 mm Hg (10.6 kPa),  $HCO_3$  24 mEq/L (24 mmol/L), base deficit -3
- Complete blood cell count: White blood cells (WBC) 22,600/ $\mu$ L ( $22.6 \times 10^9/L$ ), hemoglobin 19.8 g/dL (198 g/L), hematocrit 54%, platelets 460  $\times 10^3/\mu$ L ( $460 \times 10^9/L$ )

#### Laboratory Studies (Day 11)

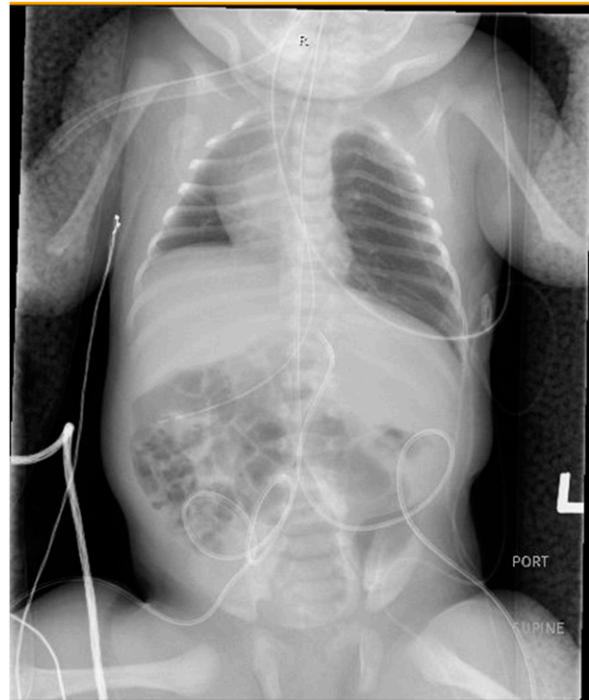
- Complete blood cell count: WBC 40,300/ $\mu$ L ( $40.3 \times 10^9/L$ ), hemoglobin 14.9 g/dL (149 g/L), hematocrit 38.3%, platelets 751  $\times 10^3/\mu$ L ( $751 \times 10^9/L$ )
- Howell Jolly bodies: Present

#### RADIOGRAPHIC STUDIES

Umbilical arterial catheters (UAC) and umbilical venous catheters (UVC) were placed and a chest radiograph was obtained to confirm the position of the endotracheal tube and the central lines (Fig).

#### DIFFERENTIAL DIAGNOSIS

- Hypoplastic right lung
- Paralyzed right dome of the diaphragm



**Figure.** Infant's initial chest and abdominal radiograph, which was obtained for confirmation of endotracheal tube positioning, as well as placement of umbilical venous and arterial catheters. The radiograph also shows hyperexpansion of the left lung, midline liver, and dextrocardia.

- Left congenital lobar emphysema
- Obstructive mass causing localized pulmonary hyperinflation
- Bronchopulmonary sequestration

#### ACTUAL DIAGNOSIS

##### Left Congenital Lobar Emphysema

Radiography of the chest revealed an endotracheal tube in appropriate position, with UAC tip at the level of the ninth thoracic vertebrae and UVC tip in the liver, which is midline. The heart size and contour are normal. There are 12 pairs of ribs bilaterally with wide intercostal spaces and no vertebral anomalies. There is possible mediastinal shift to the right with a hyperinflated left lung or hypo-inflated right lung. Elevation of the right dome of the diaphragm was also noted.

Echocardiography was performed on day 1 after birth in view of persistent desaturation and heterotaxy syndrome. It revealed a structurally normal heart, left atrial isomerism, interrupted inferior vena cava, and small atrial level shunt, with mostly left to right flow. Prenatally concerning azygous continuation was noted as well profiled. In addition, elevated right ventricular pressure and flattening of the interventricular septum were noted, suggestive of transitional neonatal physiology. These echocardiographic



findings did not explain the cause of the infant's respiratory distress.

To attempt to decipher the cause of the infant's respiratory symptoms, the team then performed fluoroscopy of the diaphragm, which revealed bilateral equal mobility when the infant was disconnected briefly from the ventilator. An upper gastrointestinal series revealed malrotation of the bowel. Ultrasonography of the abdomen revealed an absent spleen with a transverse liver. Computed tomography (CT) scan of the chest revealed left-sided congenital lobar emphysema (CLE).

## MANAGEMENT

A multidisciplinary team of radiologists, pediatric surgeons, and neonatologists decided to proceed with thoracotomy and left upper lobectomy at 2 weeks of age. The lung pathology revealed small airway dilation, consistent with lobar overexpansion and overinflation, which confirmed the clinical diagnosis of CLE.

After surgery, the infant had multiple failed attempts at extubation, which prompted rigid bronchoscopy and direct laryngoscopy. Tracheomalacia with severe airway collapse was observed without the endotracheal tube. Because the infant remains ventilator-dependent at 6 weeks after birth, a tracheostomy and long-term home ventilation is being contemplated.

Heterotaxy was diagnosed prenatally but in the absence of a prenatal diagnosis, the midline liver is a sign of heterotaxy syndrome. Such infants should be evaluated for congenital heart defects, malrotation of the bowel, and congenital biliary atresia because these are commonly associated. Infants with congenital cyanotic heart disease should be evaluated for heterotaxy syndrome. (1)

Thrombocytosis as a result of asplenia was noted and antibiotic prophylaxis was commenced. Genetic studies revealed a normal chromosome microarray analysis and whole exome sequencing was negative.

## WHAT THE EXPERTS SAY

The infant described in this case has many complex issues and this visual diagnosis is focused on the heterotaxy and the left CLE. Situs solitus describes a patient with normally placed abdominal viscera with the liver on the right and the stomach and spleen on the left. (1) Within the chest, the right lung is 3-lobed and the left lung is 2-lobed. In contrast, situs inversus describes a patient with abnormally placed abdominal viscera with the liver on the left and the stomach and spleen on the right. (1) Within the chest, affected patients have a right lung that is 2-lobed and the left lung is 3-lobed. The heart is

also abnormal, with the left atrium positioned on the right side and the right atrium positioned on the left side. If a patient has abdominal visceral organs and atrial positioning that is uncertain, the terms heterotaxy or situs ambiguous are used. (2)

Heterotaxy consists of 2 types:

1. The asplenia syndrome (or the right isomerism or bilateral right sidedness), characterized by bilateral superior vena cava
2. The polysplenia syndrome (or the left isomerism or bilateral left sidedness), characterized by an interrupted inferior cava in the abdomen (1)

The infant described in this case had combined features of both asplenia (absent spleen, central liver, and right-sided stomach) and polysplenia (bilateral left atria and an interrupted inferior vena cava). Malrotation and congenital heart defects are described in both. Details of the condition including its associations, genetics, and recurrence risks can be obtained from an authoritative review article. (2)

Infants with CLE can present with severe respiratory distress, which can be caused by localized bronchial obstruction. (3) Familial occurrence is reported and the left side is more commonly affected. A cause of CLE can be identified in 50% of cases, usually attributable to bronchial obstruction as a result of:

- Congenital absence of bronchial cartilage
- External compression of bronchii by aberrant vessels
- Bronchial stenosis
- Redundant bronchial mucosal flaps causing a ball valve obstruction of the airway
- Bronchial kinking with herniation into the mediastinum

Although most affected patients present with clinical findings in the neonatal period, approximately 5% of patients develop symptoms later, at 5 to 6 months of age, and other patients may not be diagnosed until childhood. CLE can affect any lobe but the left upper lobe is the most common site of involvement. The lobe that is affected is unable to function as a result of overexpansion and this leads to atelectasis of the ipsilateral healthy lobe. Clinical symptoms range from mild respiratory symptoms such as tachypnea and wheezing to severe respiratory distress and cyanosis.

Prenatally CLE can be diagnosed with ultrasonography. Postnatally, a chest radiograph can reveal a radiolucent lobe with a mediastinal shift. (3) CT can show the abnormal anatomy, whereas magnetic resonance (MR) imaging or MR angiography can reveal associated vascular lesions, which might be causing extraluminal compression. The differential diagnosis includes pneumonia with or without an effusion, pneumothorax, and cystic adenomatous malformation. (3) Symptomatic lesions are resected; this surgery is curative if the residual lung tissue is adequate. (4) Factors affecting long-term outcomes are described for congenital lung malformations and not CLE specifically. (4)

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical and imaging features of congenital malformations of the lung, including congenital pulmonary lymphangiectasia, the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid malformation, and mediastinal tumors

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**A Term Infant with Respiratory Distress at Birth**

Akshaya Vachharajani and Maja Herco

*NeoReviews* 2019;20:e428

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The online version of this article, along with updated information and services, is located on the World Wide Web at:

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# Spinal Muscular Atrophy: Past, Present, and Future

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## ABBREVIATIONS

AAV	adeno-associated virus
AAV9	adeno-associated virus serotype 9
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
ACMG	American College of Medical Genetics and Genomics
CHERISH	A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants with Later-onset Spinal Muscular Atrophy
ENDEAR	Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy
FDA	Food and Drug Administration
G-tube	gastrostomy tube
HRSA	Health Resources and Services Administration
ISS-N1	intronic splicing silencer N1
NBS	newborn screening
PCR	polymerase chain reaction
RT-PCR	real-time polymerase chain reaction
RUSP	recommended uniform screening panel
SCID	severe combined immunodeficiency
SHINE	A Study for Participants with Spinal Muscular Atrophy Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies
SMA	spinal muscular atrophy
SMN	survival motor neuron
TREC	T-cell receptor excision circle

## Practice Gaps

In December 2016, the United States Food and Drug Administration approved the use of nusinersen for the treatment of spinal muscular atrophy (SMA), a genetic disorder that is characterized by skeletal muscle weakness and atrophy. Although noncurative, intrathecal nusinersen has been shown to be effective in slowing down neuromuscular degeneration. In June 2018, SMA was added to the recommended uniform state newborn screening panel. However, its inclusion is not without controversy because SMA has wide variability in age at disease onset and no algorithm can accurately distinguish those who need early intervention from those who do not.

## Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by deletions or mutations in the survival motor neuron (*SMN1*) gene. SMA is characterized by loss of lower motor neurons (anterior horn cells) in the spinal cord and brainstem nuclei, leading to progressive symmetrical muscle weakness and atrophy. It affects approximately 1 in 6,000 to 1 in 10,000 individuals and is the most common inherited cause of childhood mortality, but this may soon change given recent developments. In December 2016, nusinersen, an antisense oligonucleotide drug, was approved by the United States Food and Drug Administration for the treatment of SMA, and in July 2018, SMA was added to the recommended uniform screening panel, a list of conditions that all states are encouraged to include in their newborn screening (NBS) panels. In this review, we begin with a brief clinical history of the diagnosis of SMA, discuss the current SMA clinical classification system, describe the current treatment, and discuss evolving treatment guidelines. We then discuss the path to include SMA in NBS programs as well as the controversies it engenders because the variability in age at symptom onset means early identification of asymptomatic patients who will not require therapy for years or decades. We also consider alternate population screening opportunities. Next, we consider experimental treatments. We conclude by supporting NBS for SMA with the caveat that a long-term follow-up registry is ethically essential to ensure that the benefits outweigh the harms for all screened infants, including those with milder and/or later-onset forms of SMA.

## Objectives After completing this article, readers should be able to:

1. Explain the indications, techniques, and limitations for newborn screening for spinal muscular atrophy.
2. Recognize the controversies associated with the introduction of new newborn genetic tests for conditions with variable presentation from the neonatal period through adult onset.
3. Describe the epidemiology, etiology, clinical presentation, clinical classification, and treatment of spinal muscular atrophy.

## INTRODUCTION

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disease caused by deletions or mutations in the survival motor neuron (*SMN1*) gene and is characterized by loss of lower motor neurons (anterior horn cells) in the spinal cord and brainstem nuclei, leading to progressive symmetrical muscle weakness and atrophy. There is wide variability in severity and age at onset. In this review, we begin with a brief clinical history of the diagnosis of SMA, discuss the current SMA clinical classification system, describe current treatment, and discuss evolving treatment guidelines. We then discuss the path to include SMA in newborn screening (NBS) programs, the controversies it engenders, and other possible screening opportunities. Next, we consider experimental treatments. We conclude by offering our own recommendations regarding screening and long-term follow-up given the current state of the science.

## CLINICAL HISTORY AND CLASSIFICATION OF SMA PHENOTYPES

Guido Werdnig of the University of Vienna presented the first case of SMA in an 1891 lecture titled “On a case of muscular dystrophy with positive spinal cord findings” and described 2 patients with progressive weakness in their lower extremities followed by tremors in their upper extremities and early death. (1)(2) Autopsies of these patients showed bilateral symmetrical loss of anterior horn cells. Johann Hoffman of Heidelberg University described patients with similar findings that year (3) and introduced the term, “Spinale Muskeltrophie” (“spinal muscular atrophy”), describing infants with progressive weakness, tremors, and death from pneumonia in early childhood. (4) Hoffman noted that these affected infants were born to healthy parents and that the same disease occurred in siblings. (4) Half a century later, Wohlfart et al (5) and

Kugelberg and Welander (6) described milder forms of SMA. In 1961, Byers and Banker provided the first classification of SMA, dividing patients into 3 groups (7):

Group 1: Intrauterine presentation or clinical signs in the first 2 postnatal months characterized by early weakness and early death

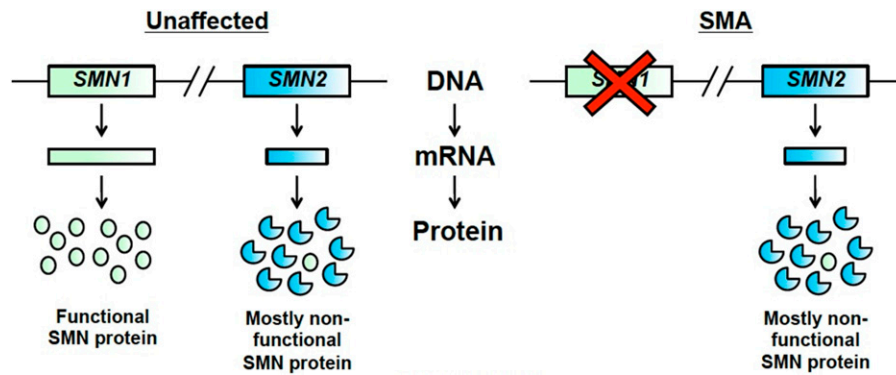
Group 2: Initial presentation between 2 and 12 months of age with more localized weakness and longer survival

Group 3: Presentation after 1 year of age

In 1992, a classification system was adopted in which different types of SMA were designated by the highest level of function (ie, sitting or standing). (8)

Today, we know that SMA is an autosomal recessive disorder that occurs in 1 in 6,000 to 1 in 10,000 individuals and is caused by loss of the SMN protein, which is encoded by the gene *SMN1*. (9)(10) The loss of *SMN1* causes SMA, with approximately 95% of affected individuals having homozygous deletions of *SMN1* exon 7. (10) Most of the remaining 5% of patients with SMA are compound heterozygotes for an *SMN1* deletion and *SMN1* point mutation. (10) Though not discussed further in this review, there are other forms of pediatric motor neuron dysfunction that are not caused by *SMN1* mutations. (10)(11)(12)

Although SMA is diagnosed by the presence of deletions and mutations in *SMN1*, the variability in clinical presentation depends on the presence of an adjacent and nearly identical gene, *SMN2*. (13) Both *SMN1* and *SMN2* genes can produce the full-length SMN mRNA transcript required to make normal SMN protein, along with other more unstable transcripts (Fig 1). However, while the full-length transcript is the major product of *SMN1*, *SMN2* produces smaller amounts of the full-length SMN mRNA transcript and hence smaller amounts of full-length (functional) SMN protein. (13)(14)



**Figure 1.** *SMN1* and *SMN2* genes and their respective mRNA transcripts and protein products. In the case of *SMN2*, mostly nonfunctional SMN protein is made but there is a small amount of functional protein. (Reprinted with permission from Dr. James Sleight, Spinal Muscular Atrophy UK website. <https://smauk.org.uk/blog/treatments-research/splicing-exons-and-the-smn2-back-up-gene>.)

In general, the more copies of *SMN2* that exist in a patient with SMA, the milder the symptoms. Without *SMN2* copies, the loss of *SMN1* function would be lethal whereas individuals with 5 or more copies of *SMN2* may have no symptoms at all. (15). However, the *SMN2* copy number does not completely correlate with phenotype, even within families. (10) (13) The current classification of SMA is determined by clinical manifestations (Table 1) based on highest attainment of function. (10)(16) SMA type 0 is the most severe form, often presenting with weakness in utero or at birth.

Patients with SMA type 1 present in the first few months of age with symmetrical limb weakness, intercostal muscle weakness, tongue fasciculations, and absent deep tendon reflexes. In contrast, affected patients have normal sensation (as is true for all forms of SMA). Untreated, these children never achieve the ability to sit. They have weak cries and difficulty handling oral secretions. Feeding becomes difficult and failure to thrive is common. Many have gastroesophageal dysmotility and gastroesophageal reflux disease, which can be life-threatening because of the risk of aspiration. As weakness progresses, decisions must be made about feeding methods, such as placement of a gastrostomy tube (G-tube) and the extent of ventilatory support. Historically, most of these children died in the first few years of age, but with the development of new therapies, the natural history is expected to evolve. Similar to all patients with SMA, patients with this type have intact cognition. (7)(8)(10)(16)

SMA type 2 is less severe than SMA type 1, with affected infants often presenting between 6 and 18 months of age. Although motor milestones are delayed, children with type 2 usually achieve the ability to sit, but cannot stand or walk independently. Respiratory issues ensue but are less severe than in patients with SMA type 1; most patients with SMA type 2 will require nighttime ventilation. Feeding and

swallowing difficulties are also common. Joint contractures develop over time from lack of movement. Many patients develop kyphoscoliosis, which exacerbates underlying respiratory dysfunction and leads to bracing or surgery. (7)(8)(10)(16)

SMA type 3 is an even milder form than SMA type 2, typically presenting after 18 months. Affected children achieve independent walking but most lose the ability over time (ranging from childhood to midlife). Scoliosis, falls, muscle and joint pain, and fatigue with activity are common. Less common are swallowing dysfunction and/or feeding difficulties. (10)(16)

Patients with SMA type 4 can present in adulthood, but, again, there is a wide range in the variability of onset of motor symptoms. Individuals with SMA type 4 can be ambulatory for decades, and they rarely experience respiratory or gastrointestinal symptoms. (10)(16)

Although the phenotypic descriptions of SMA focus on muscle weakness, hypoventilation, and gastrointestinal problems, now that patients with SMA are surviving longer, we are learning of other symptoms—disrupted sensory pathways, cardiac arrhythmias, vascular defects such as distal digital necrosis, decreased bone mineral content, and abnormal glucose metabolism—that indicate that low SMN levels affect other organ systems. (17)

## MANAGEMENT

Before 2017, the management approach in patients with SMA was supportive, with more invasive interventions (tracheostomy for airway protection and G-tube to address feeding difficulties) recommended in those with greater weakness. The 2007 consensus statement summarized the recommended approach to manage patients with SMA. (18) The guidelines recommended that patients with pulmonary disease, identified as the major cause of

**TABLE 1. Spinal Muscular Atrophy (SMA) Classification Scheme (10)(13)(16)**

CHARACTERISTICS				NATURAL HISTORY WITHOUT TREATMENT	
SMA TYPE	TYPICAL AGE AT ONSET	TYPICAL # OF SMN2 COPIES	FREQUENCY	HIGHEST MOTOR FUNCTION EVER ATTAINED (EPONYMS INCLUDED, THOUGH USED LESS FREQUENTLY)	TYPICAL AGE AT NATURAL DEATH (WITHOUT INVASIVE MEDICAL SUPPORT)
0	Prenatal/birth	0-1	<5%	Presents in the fetal and neonatal period with lack of fetal movement, contractures and severe hypotonia Early death without aggressive supportive intervention beginning at birth or shortly thereafter	Neonatal period
1	0-6 mo	1, 2 <sup>a</sup> , 3	~60%	Werdnig-Hoffman disease: Never sits independently	<2 y
2	6-18 mo	2, 3 <sup>a</sup> , 4	~10%	Dubowitz disease: Able to sit; never able to walk independently	>2 y
3	>18 mo	3 <sup>a</sup> , 4 <sup>a</sup>	<5%	Kugelberg-Welander disease: Shows marked variability in onset, symptom progression and function, but at some point are able to stand or even walk independently	Normal life expectancy
4	>21 y	≥4	~20%	Presents in adulthood. Able to walk independently (individuals with >6 copies may be phenotypically normal)	Normal life expectancy

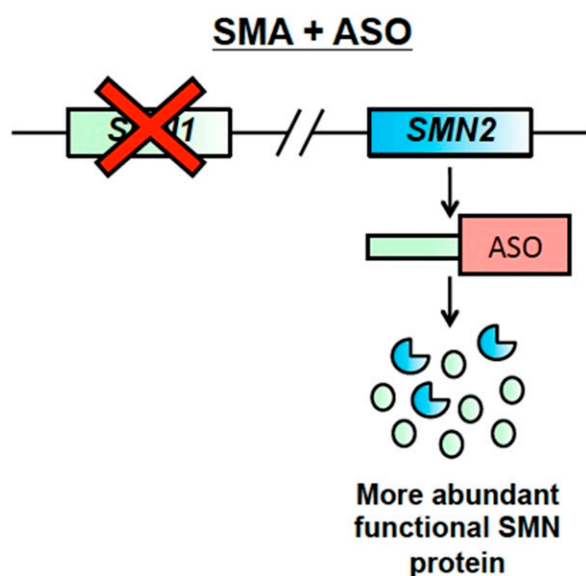
<sup>a</sup>The most frequent copy number for the SMA type (50) (see Table 2).

morbidity and mortality in SMA types 1 and 2, should receive a stepwise introduction of interventions, beginning with routine airway clearance with cough assistance and, with ongoing evidence of hypoxemia, progress to nocturnal, then continuous, noninvasive ventilation. Finally, invasive tracheotomy for chronic mechanical ventilation may be considered, “a decision that needs to be carefully discussed if requested by parents.” (18) The guidelines noted that feeding and swallowing difficulties were common in patients with SMA types 1 and 2. Clinicians were encouraged to optimize efficiency of feeding, manage gastroesophageal reflux disease, and treat abdominal distention resulting from infrequent bowel movements. However, the guidelines did not reach a consensus regarding when to refer a patient for G-tube placement.

In December 2016, the US Food and Drug Administration (FDA) approved the use of intrathecal nusinersen, the first medication designed to specifically treat patients with SMA by increasing the amount of SMN protein. The development of nusinersen began in 2004 with the identification of the intronic splicing silencer N1 (ISS-N1) sequence, which affects exon 7 skipping during splicing. (19) In 2010, Ionis Pharmaceuticals (Carlsbad, CA) was granted an exclusive

license by the University of Massachusetts Medical School, the patent holder, to develop a drug to treat patients with SMA that was based on the ISS-N1 target. (19)(20) Nusinersen is an antisense oligonucleotide designed to block ISS-N1, altering SMN2 splicing to include exon 7, producing more full-length transcripts and greater quantities of normal SMN protein (Fig 2). The efficacy of intrathecal nusinersen was first shown in the ENDEAR (Efficacy and Safety of Nusinersen [ISIS 396443] in Infants with SMA) study, a randomized controlled trial of patients with SMA type 1 younger than 7 months at the time of first administration of nusinersen or sham intrathecal injection. (21) Interim analysis found that 41% of patients treated with nusinersen were “motor milestone responders” (showing gains such as full head control, rolling, and sitting) versus 0% in the sham treatment arm ( $P<.001$ ). (21)

The sponsors sought rapid approval based on rare disease status. They submitted data from 5 trials of nusinersen. The FDA approved nusinersen on December 23, 2016, with data from fewer than 200 patient-subjects and using surrogate endpoints rather than final endpoints. (22) (23) At the time of approval, follow-up of at least 6 months' duration was available for only 78 (63.9%) of a planned 122 patients in



**Figure 2.** The antisense oligonucleotide (ASO), nusinersen, alters the mRNA transcript produced by *SMN2* to create normal protein. (Reprinted with permission from Dr. James Sleight, Spinal Muscular Atrophy UK website, <https://smauk.org.uk/blog/treatments-research/splicing-exons-and-the-smn2-back-up-gene>.)

the ENDEAR study. (23) The FDA approved nusinersen use in all classes of SMA, though clinical trial benefit was only shown in SMA type 1, and so degree and longevity of benefit for those with milder phenotypes was unknown. Since approval, additional data support the effectiveness of nusinersen in slowing (but not stopping) disease progression in SMA type 1. (24)

Additional data also show efficacy of nusinersen for treating patients with SMA types 2 and 3. Chiriboga and colleagues performed a phase 1 escalating dose trial of nusinersen in children aged 2 to 14 years with SMA types 2 and 3. (25) Patients who received the highest dose had some improvement in the Hammersmith Functional Motor Scale–Expanded during a period when it would be expected that the children’s motor development would be flat or falling. (25) Although not available at the time of the FDA review, interim and final analyses data from CHERISH (A Study to Assess the Efficacy and Safety of Nusinersen [ISIS 396443] in Participants with Later-onset SMA) found that patients aged 2 to 12 years with types 2 and 3 SMA who received nusinersen had greater improvements in motor function than those in the control arm. (26) After FDA approval, children enrolled in ENDEAR, CHERISH, and other nusinersen trials were eligible to participate in a phase 3 extension study named SHINE (A Study for Participants with SMA Who Previously Participated in Nusinersen [ISIS 396443] Investigational Studies [NCT02594124]) in which all participants received nusinersen. Data presented at the

2018 American Academy of Neurology meeting showed continued safety and benefit. (27) Long-term follow-up is critical to determine if treatment continues to slow progression, if patients experience different effects depending on their disease severity, and if potential harms manifest over time. (22)(24)

Biogen has priced nusinersen at \$125,000 per dose. The regimen requires 6 intrathecal doses in year 1 and 3 intrathecal doses annually thereafter. Gerrity and colleagues note that patients may be at risk from unrecognized harms and burdens of paying for medications because of insufficient research. (23) Insurers may require documentation of disease stability or improvement, or at least a slower deterioration of muscle function than would be expected without treatment. The prior authorization process is complex, putting children at risk with delayed treatments, and exposing families to large out-of-pocket expenses. Already, several US insurers have declined requests for SMA types 3 and 4 because this regimen is still experimental for these types. (24)

The financial expense of the drug is only part of the cost. The intrathecal mode of therapy requires families to travel to centers that administer intrathecal infusions. There are wide differences in drug administration, with some centers administering the infusion in a clinic setting and others providing sedation in an operating room setting with continuous monitoring for respiratory and hemodynamic status both during and after the infusion. Access to the patient’s intraspinal space may become limited over time as a result of disease progression and/or repeated lumbar punctures. There are also concerns about the safety of multiple lumbar punctures in patients with significant comorbidities and the costs in terms of manpower, clinical resources, and cost of drugs. (22)(28)

With the approval of nusinersen and with promising early results from other experimental drug trials, new consensus care guidelines were developed and published in 2018. (29)(30) The guidelines provide detailed recommendations for physical therapy and rehabilitation, orthopedic care, nutrition, pulmonary care, and other organ involvement. As in the 2007 guidelines, (18) respiratory management and palliative care were the 2 most controversial issues. Tracheostomy ventilation is still described as “a decision focused individually on the clinical status, prognosis, and quality of life based on discussions with the family.” (30) Although there was no consensus about the role and timing of palliative care, especially in light of the most recent therapeutic approaches, the statement encourages the dismissal of “the dichotomous model,



which sets active treatment against palliative care in favor of a model of complementarity.” (30)

## NEWBORN SCREENING FOR SMA

Current research provides strong evidence that patients with SMA type 1 have irreversible motor neuron loss early in the perinatal period, which progresses to severe denervation in the first 3 months of age and a motor unit loss of more than 90% within 6 months of age. (31)(32) A delay in diagnosis is common; studies have shown that while the onset of symptoms occurs at a mean age of 2.5, 8.3, and 39.0 months for SMA types 1, 2 and 3, respectively, the diagnosis of SMA was confirmed later at weighted mean ages of 6.3, 20.7, and 50.3 months for types 1, 2, and 3, respectively. (33) Because animal and human studies found best outcomes when treatment was provided early in the disease course, (21)(32)(34)(35) newborn screening (NBS) is regarded as the best means to avoid the diagnostic odyssey reported by many families. (36)

However, NBS is not without controversy. The quest to include testing for SMA in NBS began over a decade ago with the development of the recommended uniform screening panel (RUSP). This panel was developed in 2005 through a joint effort between the American College of Medical Genetics (now the American College of Medical Genetics and Genomics) (ACMG) and the Health Resources and Services Administration (HRSA) and contained a list of disorders for which all newborns should be screened. (37) The ACMG/HRSA evaluated 81 conditions for inclusion in the RUSP based on the ability to perform a screening test, confirm the diagnosis, and treat the disorder. SMA was not on this list of potential conditions because no screening test and no treatment existed for SMA. Despite the controversies surrounding the process, (38)(39) 25 conditions and 29 secondary conditions were selected for the RUSP. (37) The RUSP was quickly endorsed by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), which has since agreed that a transparent evidence-based approach was necessary in considering additions to and removals from the RUSP. (38)(39)

In 2008, the ACHDNC was asked to consider SMA for inclusion. The ACHDNC concluded that it was premature to even conduct an evidence-based review because no effective treatments existed. (40) The technology for efficient population screening, not available at the time of the ACMG/HRSA report, had been developed. (41) In 2006, Pyatt and Prior had demonstrated the feasibility of population screening for SMA using real-time polymerase chain reaction (RT-PCR) as first-tier testing, which identified *SMN1* exon 7 deletions with sensitivity and specificity of 100%. (41) A

concurrently run assay detected *SMN2* copy numbers. However, at that time, “the use of DNA as a testing substrate and molecular techniques for deletion analysis” (41) as initial (first-tier) screening was rarely being used, but rather, was reserved for second-tier tests performed after metabolic screening. For example, molecular genetic testing for cystic fibrosis is conducted only after a newborn is identified as having elevated immunoreactive trypsinogen levels on the NBS blood spot.

This attitude toward first-tier molecular testing changed in May 2010 with the approval of severe combined immunodeficiency (SCID) into the RUSP. (42)(43) First-tier screening for SCID is based on RT-PCR assays on DNA samples extracted from dried blood spots to measure T-cell receptor excision circles (TRECs), a byproduct of T-cell development. The need for state public health programs to adopt and implement new laboratory methodologies caused delays, and it was not until December 20, 2018, that all states had implemented SCID into their NBS program. (43)

In 2015, Taylor and colleagues modified a multiplexed RT-PCR TREC assay to allow concurrent testing of the presence or absence of the *SMN1* gene from a dried blood spot. (44) This promised to streamline the adoption of SMA into NBS programs by using already existing molecular equipment and workflows. An early pilot study in 2013-2014 by Swoboda, funded by the National Institute of Child Health and Human Diseases, was hampered by regulatory issues about whether the study could be done as an opt-out or required written consent (with different methodologies used in Utah and Colorado), and only managed to screen 16,736 infants (with no positive results), (45) despite the fact that research with parents in these two states supported an opt-out approach which would have garnered much greater participation. (46)

However, in 2017, 2 pilot NBS programs reported their experiences using PCR methods to screen newborns for SMA. Chien and colleagues described outcomes in 120,267 infants born and tested for SMA between November 2014 and September 2016 at the National Taiwan University Hospital Newborn Screening Center. (47) Of the 15 infants who screened positive, 8 were false positive for the disease (identified later as carriers) and 7 were diagnosed with SMA. In those diagnosed, 3 patients had 2 copies of *SMN2*, 2 had 3 copies, and 2 had 4 copies. The duration of patient follow-up ranged from 1.5 to 25 months. Some patients received treatment with nusinersen under a research protocol. In the 3 patients with 2 *SMN2* copies, 1 is currently receiving nusinersen, 1 died, and 1 patient’s family has declined participation in research. In the 2 who have 3 *SMN2* copies, 1 is receiving nusinersen and is well at 11 months and the other is not receiving nusinersen and lost ambulation at 17 months. The 2 patients who have 4 *SMN2* copies had

normal examination findings and were not receiving nusinersen at their last follow-up.

The second pilot study was reported by Kraszewski and colleagues and took place in 3 hospitals in New York City. (48) From January 2016 to January 2017, 3,826 (93% of eligible infants who were approached for consent) participated in a study to assess the ability of NBS to diagnose patients with SMA. Of the infants, 94.6% were screened as negative and did not require additional testing. The researchers identified 59 carriers and 1 infant homozygous for the *SMN1* exon 7 deletion who was immediately enrolled in a nusinersen trial. At 1-year follow-up, she had received 6 doses of nusinersen and was meeting all of her developmental milestones. (48)

In December 2016, nusinersen was approved by the FDA for the treatment of all types of SMA. In February 2017, armed with NBS pilot data and a therapy, Cure SMA (a national nonprofit support and advocacy organization for patients and families with SMA) reapplied to have SMA included in the RUSP. Because virtually all states were screening for SCID, (44) the infrastructure for first-tier molecular genetic testing for SMA was in place. The ACHDNC agreed to reevaluate the evidence and nominated it for inclusion into the RUSP in February 2018. This was approved 4 months later by the Secretary of the Department of Health and Human Services. Even before it was included in the national RUSP, 4 states were already screening newborns for SMA. (49)

SMA NBS avoids delays in diagnosis and allows treatment to be initiated before permanent axonal loss takes place. Cure SMA convened a group of experts to develop guidelines for initiating treatment in those identified with SMA by NBS and based treatment initiation on *SMN2* copy number because this is the best predictor of symptom onset and clinical severity. (32) The decision to treat infants with 1 copy of *SMN2* was deferred to the treating physician and family because these infants are likely to have SMA type 0 and may already show significant weakness at birth. In this setting, axonal damage may already be irreversible. In contrast, for infants with SMA type 1 (or patients who had 2 or 3 copies of *SMN2*), the guidelines recommend immediate treatment. (32) This is likely to result in overtreatment because copy number only roughly correlates with phenotype and some children who would not experience any symptoms for years will begin treatment as infants.

Another question that arises from early testing is: What proportion of infants with SMA with 3 *SMN2* copies will have a type 3 phenotype? Calucho and colleagues reviewed data from 625 unrelated Spanish patients and 2,834 patients identified from the literature (Table 2). (50) Most patients

(2,416 of 3,459 or 70%) had SMA type 1 or 2, and most of those with type 1 had only 1 or 2 copies of *SMN2* (1,007 of 1,256 or 80%). However, a person with 3 *SMN2* copies could present as type 1, 2, or 3 and in fact, a person with 3 *SMN2* copies has a 31% chance (515 of 1,662) of having SMA type 3, (50) which usually presents sometime in childhood, with some children having mild symptoms. (10)(16) It is important to monitor treated and untreated patients to determine whether those patients who truly require early treatment can be separated from those who will incur risks without benefit. Costs should be considered as well; the drug is far too expensive for the health care community to blindly treat all patients with a diagnosis of SMA. It is important to identify patients (as early as possible) who are unlikely to benefit from the medication.

If treatment is deferred in affected infants with 3 or more copies, changes in physical examination findings, including loss of tendon reflexes or other concerns of weakness, should trigger the need to start nusinersen treatment quickly. (32) Follow-up at a specialized pediatric neuromuscular clinic is essential to assess for subtle changes.

Consensus is lacking on how often patients with 4 or more *SMN2* copies should be followed and when, if ever, to start nusinersen treatment. In Taiwan's NBS pilot program, Chien and colleagues did not recommend routine clinical neurology follow-up for infants with 4 or more *SMN2* copies, but told families to return if symptoms develop. (47) In contrast, Kraszewski and colleagues were equivocal about what to do for children with 4 or more copy numbers: "it is still unclear whether patients with more than 4 *SMN2* copies should be treated as newborns and how frequently they should be treated. We believe it is likely that such children would derive benefit, but it is unclear exactly what the optimal treatment protocol should be." (48)

## CLINICAL CONTROVERSIES ARISING FROM EARLY DIAGNOSIS AND TREATMENT

The first controversial issue about using NBS to diagnose patients with SMA is that the methodology for early diagnosis might miss some cases of SMA. Most states are considering methods based on detection of homozygous deletions of *SMN1* exon 7, which will overlook some infants with SMA who are heterozygous for *SMN1* deletion and also have a point mutation. Thus, this cohort may not be diagnosed until symptoms develop, which would delay treatment.

As alluded to earlier, whom to treat soon after early diagnosis is controversial. If expert guidelines recommend "immediate treatment" for an infant who has 2 or 3 *SMN2*

TABLE 2. **Summary of Combined Data on Types of Spinal Muscular Atrophy<sup>a</sup>**

SMN2 COPY NUMBER	TYPE 1 (N=1,256) N (%)	TYPE 2 (N=1,160) N (%)	TYPE 3 (N=1,043) N (%)
1	88 (7)	4 (<1)	0 (0)
2	919 (73)	192 (16)	54 (5)
3	245 (20)	902 (78)	515 (49)
4	3 (<1)	59 (5)	455 (44)
5	1 (<1)	3 (<1)	16 (2)
6	0 (0)	0 (0)	3 (<1)

<sup>a</sup>Data extracted from articles published from 1999 to date.

Reprinted with permission from Calucho M, Bernal S, Alias L, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord.* 2018;28(3):208–215. (50)

copies, then some infants with SMA type 3 will be treated even though they may not present for years and their progression may be slow. Given the cost of the drug and its invasive administration, this will mean excessive treatment for some. Based on the data from Calucho and colleagues, in the 2,827 infants with 2 or 3 SMN2 copies, 569 or 20.1% were diagnosed as having SMA type 3 (50).

Some identified with NBS may not present until adulthood. The number is generally assumed to be small because SMA type 4 is considered a relatively rare presentation, (10)(16) (50) However, as population screening becomes more commonplace, the number of individuals diagnosed with adult-onset disease is likely to rise. This is because many of these individuals may have never been diagnosed and therefore not included in the medical literature or in databases. Current pediatric genetic testing guidelines discourage early diagnosis of children with adult-onset conditions because it takes away their right to decide for themselves whether they want to get tested and their right to privacy about their adult health risks. It also exposes them to the risks that they will be treated as if they are ill even while asymptomatic (“vulnerable child syndrome”). (51)(52)(53)(54)

The following logistical challenges arise from identifying infants with adult-onset conditions: 1) how to ensure that individuals asymptomatic in childhood are aware of their diagnosis; 2) how to ensure that health information diagnosed at birth is available to their adult physicians; and 3) how to establish and maintain the infrastructure needed to ensure that this information follows these individuals for life so that they might benefit from early treatment if and when their symptoms appear. (51)(55)(56)

Expecting asymptomatic patients to pass on this information to clinicians during adulthood is unrealistic because it assumes that their parents informed them about the diagnosis, that patients know to share this information with all of their physicians, and that they are aware of symptoms that should lead to further evaluation. This is further complicated in the patchwork health care system that exists in the United States.

A major controversy of early SMA diagnosis arises in children who are eligible to be treated but the family is unwilling to have their child treated. This may be especially concerning if the clinicians involved feel a sense of urgency to start treatment when it can be the most effective. It is important for clinicians to understand why a family refuses treatment and to make sure that the family is cognizant of the risks and benefits of forgoing medication. Some parents may refuse treatment because of lack of sufficient information, lack of long-term safety data, risks related to repeated lumbar punctures, and repeated anesthesia exposure. Some may want to participate in other treatment trials or to delay treatment to see if symptoms are likely to develop (some infants with 3 SMN2 copies may not develop symptoms for years). Others may refuse because of financial and logistical burdens if they live far from administration sites or the administrative sites are out of network, which would require negotiation with insurers and possible large out-of-pocket expenses. We believe it is premature to argue that refusal in the first weeks after birth is inherently medically neglectful. However, parents must be counseled about the risks and benefits of delaying treatment and signs and symptoms of disease progression that should trigger immediate follow-up.

The use of ventilation in symptomatic children is also controversial. Although we hope that with early diagnosis and treatment, children with SMA will never have to face the need for invasive ventilation, there are many children with SMA who progress or are already too weak to benefit from the many advances described. The consensus for the use of noninvasive ventilation, including airway clearance using mechanically assisted coughing for infants with SMA is unanimous; however, the data show that a significant percentage of physicians did not support more invasive tracheostomy and ventilation. (57)(58)(59)(60)(61) Physicians have raised concerns about the quality of life of children receiving ventilation, because it often removes their ability to speak. Given that this disease is also associated with bulbar weakness, individuals receiving ventilation may have severely limited communication abilities. (62)(63) Still, it should be noted that numerous studies show that patients and parents view quality of life for those with disabilities as much better than their physicians rate them. (64)(65)(66)(67)

A final question is whether NBS is the appropriate time to screen for SMA. An alternative strategy is prenatal screening to inform parents of health risks to the fetus as early as possible or even preconception screening to provide couples with reproductive options. Carrier frequency varies by race/ethnicity, occurring in 1 in 40 Asians, 1 in 50 whites, 1 in 100 blacks, and 1 in 76 Hispanics. (68)(69)(70) That is, SMA is relatively frequent in all ethnicities. SMA carrier screening has been supported by the ACMG since 2008 (71) and by the Association for Molecular Pathology since 2011. (72) In 2009, the American College of Obstetrics and Gynecology supported targeted testing of those with a family history, (73) but since 2017, this organization supports offering universal prenatal screening in all ethnic communities. (74) Whether couples offered screening will take advantage of this option, and, if testing is done, how they will use the information, is not yet known. Clearly, counseling will need to discuss the diverse phenotypes as well as the current and developing treatments. All professional societies support parental and prospective parental rights to nondirective counseling and freedom in reproductive decision making. (71)(72)(74)

Of course, the ideal timing of screening for SMA may not be either during the prenatal/periconception or neonatal period but rather, screening might be best if offered in both periods because they serve different purposes. (75) Prenatal/periconception screening provides couples with reproductive options. These types of screenings should be voluntary with pre- and postnatal counseling. NBS, in contrast, serves to provide information about health conditions affecting

infants, and fairness demands that it be universally provided to allow for maximal benefit to the infant, especially when life saving treatments exist.

## THE FUTURE

Although nusinersen was initially the only therapy approved for SMA, many other therapies are under development. Gene replacement therapy is being developed, which uses self-complementary adeno-associated virus (AAV) serotypes that cross the blood-brain barrier and can target brain cells. (76)(77)(78) In October 2018, AveXis (Chicago, IL) filed for FDA approval for single-dose intravenous infusion of AVXS-101. AAV serotype 9 (AAV9), in particular, shows active transport across the blood-brain barrier as well as high transgene expression and spread in the central nervous system, with particular tropism for motor neurons. (76) Animal studies using AAV9-mediated delivery of *SMN1* confirmed that transgene expression is stable after a single dose and successfully corrected the phenotype in the mouse model. (78)

Based on this work, a phase 1 trial was conducted in infants with SMA type 1 using AAV9 carrying *SMN1* (the modified virus called AVXS-101), and recently reported by Mendell et al. (79) The first cohort of 3 patients (mean age 6.3 months) received a low dose and the next 12 patients (cohort 2; mean age 3.4 months) received a higher dose. Follow-up at a median age of 27.8 months and 30.7 months for patients in cohorts 2 and 1, respectively, found all patients alive and without need for permanent ventilation. (80) In follow-up, the patients in cohort 2 showed a reduced need for nutritional and ventilatory support and improvement in swallowing function. Of the 12 patients in cohort 2, 11 (92%) could feed orally, with 6 (50%) able to maintain full nutritional needs with oral feedings exclusively, and 11 (92%) able to speak. (80) These were remarkable outcomes after a single-dose trial, given the natural history of SMA type 1.

These outcomes prompted AveXis (owned by Novartis, Basel, Switzerland) to submit a biologic license application with the FDA to allow for the marketing of AVXS-101 to treat SMA. The FDA accepted the application for priority review in October 2018; and on May 24, 2019, Zolgensma (onasemnogene abeparvovec-xioi), was the first gene therapy approved to treat children older than 2 years of age with an expected price tag of 2.125 million dollars. (81) Similar applications have been submitted in Europe and Japan and await approval.

Animal models of SMA have suggested that the intravenous delivery of AAV9 may work best in animals at an early developmental stage (76)(78); intrathecal delivery of AAV9 requires less volume and less total dose of the drug and has been promising in animal models of SMA. (82) AveXis is

currently sponsoring a phase 1 clinical trial of intrathecal AVXS-101, which is a potentially useful route for older and heavier patients who would otherwise require large volumes with the weight-based intravenous dosing. (82)

Apart from direct replacement of the *SMN1* gene, there have been other avenues of drug development for patients with SMA, primarily looking at small molecules that have nonspecific actions such as muscle preservation, neuroprotection, or target *SMN2* splicing. (83) A neuroprotective agent considered promising for SMA was olesoxime, which interacts with mitochondrial membranes to preserve mitochondrial function. (84)(85) It had been studied for several years but in 2018, Roche Holding AG (Basel, Switzerland) announced that they were halting further development. (86) Outcome data in SMA type 2 and nonambulatory patients with SMA type 3, which were initially promising at 12 months, (84) showed declines in motor function of treated patients at 18 months. (85)

The efficacy of nusinersen has prompted additional investigation into other agents that might affect SMN type 2 before mRNA splicing. (87) Two promising agents have been identified: risdiplam (formerly, RG7916) (88)(89)(90) and brana-plam (formerly LM1070). (87) Both agents can be administered orally, providing many potential advantages over the cumbersome intrathecal delivery of nusinersen. Given the prominent loss of muscle that results in motor neuron disease, 2 agents that prevent muscle atrophy are in early stages of testing. Reldesemtiv (also called CK-2127107) activates troponin in fast skeletal muscle and appears to improve muscle force and exercise tolerance. (83)(91)(92)(93) SRK-015 is a monoclonal antibody that inhibits myostatin (a muscle growth inhibitor), and in animal models, SRK-015 has been shown to increase muscle mass. (94)

## HOW TO ETHICALLY PROCEED WITH SMA NBS

SMA testing as part of mandatory NBS warrants several ethical considerations. There needs to be a plan to follow the 15% or 20% (or more) of infants who test positive but are asymptomatic and may not require treatment for years or decades. Late-onset and milder phenotypes may be even more common than we currently believe. Thus ethically, comprehensive long-term follow-up databases are needed. We must acknowledge that for some individuals, the harms of predictive information and the psychological and emotional costs that they cause, as well as the potential harms of unnecessary or even inappropriate treatment that parents may impose on their children, may outweigh the diagnostic benefit, particularly because treatment benefit for late-onset presentation has not yet been proven.

The variability in clinical presentation of patients with SMA also supports the importance of more research on the psychosocial harms and benefits of informing parents at birth that their infant is at risk for a late-onset health problem. (22) This diagnostic approach creates patients in waiting with all the psychosocial risks and harms that this can cause, including unnecessary invasive testing and treatment. (95)

Unfortunately, the type of comprehensive and publicly transparent follow-up registry that is needed has traditionally been difficult to develop and maintain. (96)(97) It is imperative that national and international data are collected to understand the impact of screening and treatment. Because of the rarity of this disease, the data need to be collected in such a way as to combine information from the various registries around the world.

## CONCLUSION

Much progress has been made in understanding, diagnosing, and treating SMA since it was first described in 1891. While the only currently available treatment is nusinersen, other treatments may be available soon. Both the cost of treatment and the timing of initial therapy raise concerns about equitable access. Justice also requires equitable access to screening, and yet, screening is not without its problems. First, carrier screening does not pick up all at-risk individuals. Second, NBS may miss approximately 5% of infants with point mutations. Third, screening identifies at least 20% of infants who may be asymptomatic for years or decades and the psychosocial, emotional, and even clinical risks and benefits of such knowledge have not been well-studied. A long-term follow-up registry is ethically essential to ensure that the benefits outweigh the harms for all screened infants, including those with milder forms of SMA.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the basis for (including genetic) clinical and laboratory features (including associated abnormalities), differential diagnosis, evaluation, management, and outcomes of neonatal hypotonia/neuromuscular weakness.
- Recognize the controversies associated with the introduction of new genetic tests for rare and common diseases that present in the neonatal period.
- Recognize the controversies associated with the development of gene-based therapies to treat neonatal conditions.



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1. Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by loss of survival motor neuron (SMN) protein encoded by the *SMN1* gene. In 95% of affected patients, the genetic mechanism for SMA is a homozygous deletion of the *SMN1* exon 7, while the remaining 5% of cases are caused by heterozygous *SMN1* deletions or *SMN1* point mutations. The timing and severity of the clinical presentation depends on the number of *SMN2* gene copies. Which of the following statements regarding the classification and presentation of SMA is correct?
  - A. SMA type 0 presents with stillbirth, and by definition, these patients always have 0 copies of *SMN2*.
  - B. SMA type 0 is increasingly recognized as an important subtype of SMA, representing about 25% of all SMA cases.
  - C. Patients with SMA type 1 typically present immediately after birth with symptoms and patients can have 0 or 1 copy of *SMN2*.
  - D. SMA type 2, also known as Kugelberg-Welander disease, presents between 6 and 18 months of age.
  - E. In general, the more copies of *SMN2* that exist in a patient with SMA, the milder the symptoms.
2. SMA type 1 is the most common type of SMA, representing approximately 60% of all SMA cases. Despite current evidence that patients progress to severe denervation by age 3 months followed by more than 90% motor unit loss by age 6 months, delays in diagnosis remain common. What is the mean age at diagnosis in patients affected by SMA type 1?
  - A. Prenatally, usually at the ultrasound visit at 20 weeks of gestation.
  - B. 1 month.
  - C. 6 months.
  - D. 12 months.
  - E. 24 months.
3. With the approval of nusinersen by the US Food and Drug Administration (FDA) in 2016, the management of SMA has moved beyond supportive care alone. Nusinersen is an antisense oligonucleotide that prevents exon 7 skipping during splicing by blocking the intronic splicing silencer N1. This results in the production of more full-length transcripts and thereby more SMN protein. Which ONE of the following statements regarding nusinersen is correct?
  - A. In December 2016, the FDA approved nusinersen for the treatment of all classes of SMA.
  - B. In the ENDEAR (Efficacy and Safety of Nusinersen [ISIS 396443] in Infants With Spinal Muscular Atrophy) trial, an interim analysis revealed that 10% of patients with SMA type 1 treated with nusinersen were "motor milestone responders."
  - C. Patients enrolled in the ENDEAR trial had to be younger than 1 week of age at the time of first intrathecal administration of nusinersen.
  - D. Recommended treatment protocols suggest that only 1 intrathecal administration of nusinersen, with the timing suggested to be prior to 2 months of age, with a recommendation against use of the drug if the treatment has not been given by that age.
  - E. The CHERISH (A Study to Assess the Efficacy and Safety of Nusinersen [ISIS 396443] in Participants with Later-onset Spinal Muscular Atrophy) trial found no benefit of nusinersen in patients with any type of SMA, with increased adverse effects in SMA type 2.

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4. With the development of therapies such as nusinersen and the importance of early SMA diagnosis to optimize outcomes, there has been a renewed interest in including SMA in the newborn screen. Which ONE of the following statements regarding newborn screening for SMA is correct?
- A. Although there have been several pilot studies, no newborn screening program or similar work has led to any identified cases of SMA.
  - B. Carrier states cannot be identified with the current methods of screening.
  - C. Newborn screening for SMA relies on quantitative real-time polymerase chain reaction to identify *SMN1* exon 7 deletions.
  - D. The addition of SMA testing to the recommended uniform screening panel will require all states in the United States to purchase new equipment.
  - E. The methodology for SMA screening allows for the detection of all causes of SMA including heterozygous *SMN1* deletions and point mutations.
5. SMA was approved by the Secretary of the Department of Health and Human Services for inclusion in the recommended uniform screening panel in February 2018. With the recommendation to include SMA, new guidelines have been developed for the use of nusinersen in this patient population. Which ONE of the following statements regarding the use of nusinersen in patients identified via newborn screening is correct?
- A. All patients with SMA, particularly those with 4 or more copies of *SMN2*, should be followed in a specialized neuromuscular clinic every month starting at birth until 5 years of age.
  - B. Because approximately 50% of patients with 3 copies of *SMN2* will have type 3 SMA, immediate treatment with nusinersen is not recommended.
  - C. Current recommendations are to initiate nusinersen treatment immediately for all patients with 2 copies of *SMN2*.
  - D. Newborn siblings of patients who have been diagnosed with SMA should receive treatment with nusinersen prior to newborn screening as a prophylactic.
  - E. Treatment with nusinersen is contraindicated in infants with only 1 copy of *SMN2*.

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# Reducing Germinal Matrix-Intraventricular Hemorrhage: Perinatal and Delivery Room Factors

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## Practice Gaps

Much research has gone into understanding the pathogenesis and prevention of germinal matrix hemorrhage–intraventricular hemorrhage (IVH). Based on the current evidence, it is widely accepted that antenatal corticosteroid administration has helped reduce the risk of IVH in preterm infants. With continued identification of maternal interventions that can be implemented during the perinatal period, we hope to see a reduction in IVH rates. Almost half of all IVH occurs within the first day after birth, so understanding delivery room interventions that reduce IVH risk will hopefully contribute to further the ongoing efforts on reduction. At this time, prevention of premature birth continues to have the single greatest impact on reducing the incidence of germinal matrix hemorrhage–IVH.

## Abstract

Germinal matrix hemorrhage–intraventricular hemorrhage (IVH) is the most common form of brain injury in preterm infants. Although severe IVH has declined over the years, it still affects approximately 6% of infants born before 32 weeks of gestation. Most IVH cases are detectable by the first 24 hours after birth; therefore interventions to prevent IVH should focus on antenatal management for pregnant women and delivery room management. Obstetrical interventions, including antenatal corticosteroids, maternal rather than infant transport, and possibly elective cesarean delivery have been associated with a decreased risk of IVH. Neonatal interventions in the delivery room, including delayed cord clamping or umbilical cord milking, maintaining normothermia, avoiding fluctuations in cerebral blood flow, and optimal ventilation management are associated with a decreased risk of IVH. Multiple clinical trials are under way to further identify IVH risk factors, ability to monitor or predict IVH, and ideally prevent IVH altogether. This discussion will focus on reviewing current obstetric and neonatal management practices and their associations with germinal matrix hemorrhage–IVH.

**AUTHOR DISCLOSURE** Drs Lim and Hagen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
CO <sub>2</sub>	carbon dioxide
CS	cesarean section
DCC	delayed cord clamping
ELBW	extremely low birthweight
Fio <sub>2</sub>	fraction of inspired oxygen
GMH	germinal matrix hemorrhage
ICC	immediate cord clamping
IVH	intraventricular hemorrhage
NICHD	National Institute of Child Health and Human Development
NIRS	near-infrared spectroscopy
NRN	Neonatal Research Network
SpO <sub>2</sub>	oxygen saturation
UCM	umbilical cord milking
VLBW	very low birthweight

## Objectives After completing this article, readers should be able to:

1. Describe the grading of intraventricular hemorrhage.
2. Identify the antenatal factors associated with decreased risk of intraventricular hemorrhage.
3. Identify delivery room management associated with decreased risk of intraventricular hemorrhage.

## BACKGROUND

Germinal matrix hemorrhage (GMH)–intraventricular hemorrhage (IVH) is a well-described neonatal brain injury and is the most common form of intracranial hemorrhage in neonates. GMH occurs in the highly vascularized region in the developing brain known as the *subependymal germinal matrix*, an area from which precursor central nervous system cells originate. When bleeding from the subependymal region extends into the lateral ventricles, the bleeding is classified as IVH. The immature vascular network in the germinal matrix is most abundant in the fetal brain between 24 and 34 weeks' gestation. With increasing gestation, this region matures, and by term, this primitive collection of blood vessels involutes and is replaced by a mature capillary network. (1)(2)

GMH-IVH severity is graded using 1 of 2 published classification systems describing cranial ultrasonography findings. The Papile grading system was originally based on brain computed tomography images of IVH and was named according to the location and magnitude of hemorrhage. (3) As ultrasound technology improved and more cranial ultrasound scans were obtained, the Papile grading system became commonly used to also describe ultrasound images. (Fig 1). The Volpe grading system is the other major grading system and is based on cranial ultrasonography findings. (2) One main difference between the 2 systems is the definition of and pathophysiologic mechanism underlying what constitutes a grade 4 hemorrhage (Table 1).

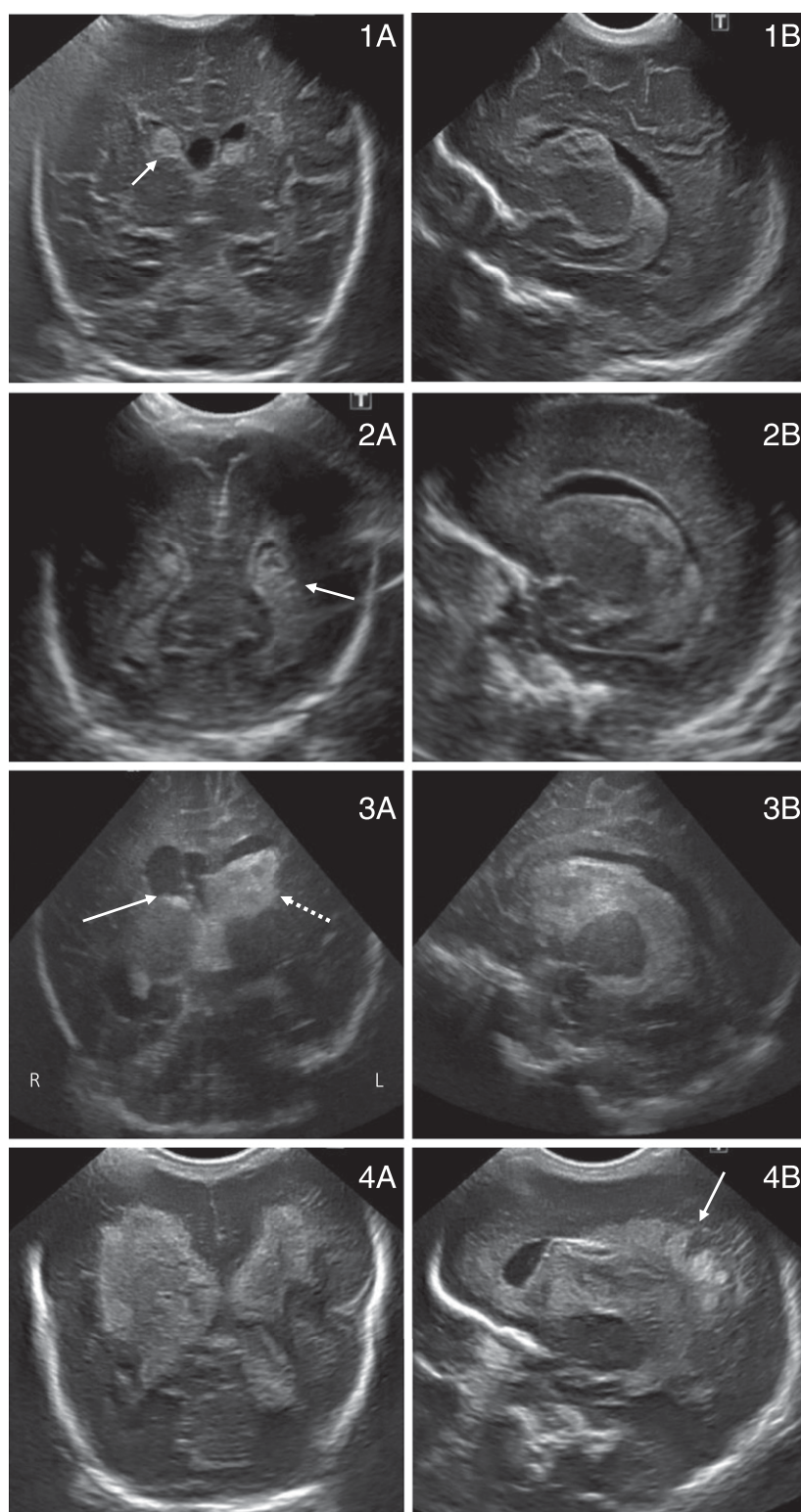
It has been well reported that the incidence and severity of IVH increases with decreasing gestational age. The normal vascular physiology of the developing brain, as outlined earlier, provides context to help explain this decrease in incidence and severity of GMH-IVH seen with increasing gestational age. According to data from the Vermont Oxford Network, based on 247,392 very-low-birth-weight (VLBW; birthweight <1,500 g) infants born between 2009 and 2013, the incidence of any grade IVH is 24% to

26%. (1) A National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) study published in 2010 looked at data for 9,575 VLBW neonates born between 22 and 28 weeks' gestation and reported the incidence of IVH at approximately 20% to 25%. (4) Fortunately, the authors also saw a reduction in the incidence of severe IVH in VLBW infants from 19% in 1993 down to 15% in 2012. (5) Again, a decline in severe IVH was also reported in a 2018 study that examined data from over 44,000 infants born at less than 32 weeks' gestation over a 10-year period; severe IVH rates decreased from 9.7% in 2005 to 5.9% in 2015. (6)

In 2014, a systematic review and meta-analysis of IVH timing in preterm infants found that almost half of IVH cases occurred within the first 6 hours after birth while 38% of cases were diagnosed after 24 hours of age. (7) By day 4 after birth, almost 90% of IVH lesions are detectable. (2) Given the early timing at which most GMH-IVH occurs, implementation of perinatal and delivery room interventions that reduce IVH may be the most impactful. The following is a review of perinatal and immediate delivery room interventions that have been clearly shown to reduce the risk of GMH-IVH in preterm infants, factors that are linked to an increased risk of developing GMH-IVH, and those interventions for which the evidence is still unclear but current investigations are under way (Table 2) (Table 3).

## ANTENATAL GLUCOCORTICOIDS

There are clear perinatal interventions that help reduce the incidence of GMH-IVH. Because the greatest risk factor for GMH-IVH development is prematurity, interventions that reduce preterm birth will also indirectly help to reduce the incidence of hemorrhage. According to the American College of Obstetricians and Gynecologists (ACOG), women who are at risk for preterm delivery within 7 days should be given antenatal glucocorticoids for induction of fetal



**Figure 1.** Cranial ultrasound images based on Papile grading system. 1A. Coronal image of bilateral grade 1 intraventricular hemorrhage with a solid arrow pointing at a germinal matrix hemorrhage. 1B. Sagittal image of grade 1 intraventricular hemorrhage. 2A. Coronal image of bilateral grade 2 intraventricular hemorrhage with a solid arrow pointing at a grade 2 intraventricular hemorrhage with blood in the ventricle and no ventricular dilation. 2B. Sagittal image of grade 2 intraventricular hemorrhage. 3A. Coronal image of left-sided grade 3 intraventricular hemorrhage and right-sided grade 2 intraventricular hemorrhage. Dashed arrow is pointing at a dilated ventricle filled with blood. Solid arrow is pointing at blood in the ventricle without ventricular dilation. 3B. Sagittal image of grade 3 intraventricular hemorrhage. 4A. Coronal image of bilateral grade 4 intraventricular hemorrhage with bleeding into the ventricles causing dilation and parenchymal hemorrhage. 4B. Sagittal image of grade 4 intraventricular hemorrhage with a solid arrow pointing at hemorrhage in the parenchyma.

maturity. (8) This practice has been shown to decrease overall neonatal mortality and morbidity. Antenatal steroid administration has also been shown to independently

decrease IVH risk as well as the severity and frequency of respiratory distress syndrome, the need for respiratory support, the incidence of necrotizing enterocolitis, and

TABLE 1. **Comparison of Intraventricular Hemorrhage (IVH) Grading Systems<sup>a</sup>**

SEVERITY	PAPILE	VOLPE
Grade 1	Germinal matrix hemorrhage	Germinal matrix hemorrhage with or without IVH (< 10% of ventricle filled with blood)
Grade 2	IVH without ventricular dilation	IVH (10%–50% of ventricle filled with blood) typically without ventricular dilation
Grade 3	IVH with ventricular dilation	IVH (>50% of ventricle filled with blood) typically with ventricular dilation
Grade 4	IVH with ventricular dilation and parenchymal hemorrhage	Periventricular hemorrhagic infarction <i>Not an extension of IVH</i>

<sup>a</sup>Mild IVH is generally defined as grade 1 or 2 and severe IVH is generally defined as grade 3 or 4.

systemic infections in the first 48 hours after birth. (9) The maturational effect of antenatal steroids on a developing fetus' organs is complex and continues to be studied.

It has become standard of care that expectant women at risk of imminent preterm delivery be given either betamethasone or dexamethasone. Both steroids have the ability to cross the placenta and have been well-studied. A recent Cochrane systematic review of over 30 studies comparing these 2 steroid regimens revealed possible increased reduction of IVH in neonates whose mothers received dexamethasone compared with betamethasone. (10) However, an NICHD NRN study of 3,600 VLBW infants who

received antenatal betamethasone versus dexamethasone found that both steroids equally reduced the risk of IVH, while betamethasone further reduced the risk of neonatal death and severe retinopathy of prematurity. (11) A follow-up NICHD NRN study comparing extremely low-birthweight (ELBW <1,000 g) infants exposed to prenatal dexamethasone versus betamethasone found that at 18 to 22 months' corrected age, ELBW infants exposed to dexamethasone were more likely to have neurodevelopmental and hearing impairments compared with those exposed to betamethasone. (12) Given these results, based on the current available evidence it is most prudent to administer antenatal betamethasone over dexamethasone to expectant women in preterm labor.

TABLE 2. **Perinatal Factors Associated with Intraventricular Hemorrhage (IVH) in Preterm Infants**

<b>Increased IVH Risk</b>
• Maternal inflammatory conditions (ie, chorioamnionitis)
• Placental abruption
<b>Decreased IVH Risk</b>
• Antenatal glucocorticoids
• Maternal medications
◦ Tocolytics in setting of preterm labor, specifically nifedipine or atosiban
◦ Antibiotics in setting of chorioamnionitis
<b>Possible Impact on IVH Risk</b>
• Maternal transport before delivery
• Delivery mode and timing
• Preeclampsia

## MATERNAL TRANSPORT

Evidence from a large multicenter retrospective study of nearly 67,600 VLBW infants demonstrated that interhospital transport within the first 48 hours after birth was an independent risk factor for IVH development. (13) Furthermore, it has been reported that the longer the duration of transport (>60 minutes), the higher was the rate of neonatal death. (14) However, a recent single-center study, which controlled for an even larger number of maternal and birth variables than the previous study, reexamined the postulated association between IVH and interhospital transport of VLBW infants and concluded that based on their findings, interhospital transport is not an independent risk factor for IVH as previously reported. (15) Thus, it is evident that further research must be done in this area to better understand the true risk of IVH associated with neonatal transport. If in fact transport does contribute to the development of IVH, it is reasonable to assume that the cause is

**TABLE 3. Delivery Room Factors Associated with Intraventricular Hemorrhage (IVH) in Preterm Infants**

<b>Increased IVH Risk</b>
• Hypothermia (moderate or severe)
• Factors that decrease cerebral blood flow
◦ Hypoxemia
◦ Hypotension (with signs of poor perfusion)
◦ Hypercapnia
• Multiple intubation attempts (in VLBW infants)
<b>Decreased IVH Risk</b>
• Delayed cord clamping (no benefit found in preventing severe IVH)
• Umbilical cord milking (no benefit found in preventing severe IVH)

multifactorial, including underlying maternal processes, degree of prematurity, severity of illness necessitating transport, thermoregulation, hemodynamic instability, maintaining optimal ventilation and oxygenation while on transport, and even the physical risks associated with transport itself. Given the possible increased risk of IVH and mortality associated with postnatal transport, in utero transport of high-risk pregnancies to a tertiary care center with a higher level NICU is preferable over the transport of critically ill neonates, especially in the first few days after birth. Current clinical trials on the effects of transportation on infants should shed light on the physiological effects of neonatal transport (PremiTrans NCT01851668, TRiPs NCT03754439).

### DELIVERY MODE AND TIMING

Currently, the impact of infant delivery mode on IVH incidence is unclear. Previous studies have not demonstrated a significant difference in risk of severe IVH among VLBW infants delivered vaginally versus those delivered via cesarean section (CS). (16)(17) However, more recent published reports point to lower IVH rates associated with preterm infants delivered via CS compared with infants delivered vaginally. (16)(18)(19) Other studies suggest an association with increased IVH rates when a pregnant woman is in active labor. (20)(21)(22) It is therefore reasonable to conclude that preterm infants delivered via CS without labor may potentially further reduce the risk of IVH. However, this decision should be made carefully,

balancing the risks and benefits to both the pregnant woman and fetus, given that CS poses significant later risks for the mother.

Another factor that may affect the risk of IVH is the time of day at which a preterm delivery occurs. A large retrospective chart analysis of over 47,600 VLBW infants has suggested that being delivered during “off-peak hours” may increase a VLBW infant’s risk of severe IVH. (23) Off-peak delivery times were between 12:00 am and 7:00 am, with the highest risk associated with those infants born between midnight and 4:00 am. The authors propose that overnight staffing levels and decline in proficiency during night hours play a role. However, other inherent biologic factors may be possibly associated with overnight deliveries that are not accounted for, which contribute to these findings. For example, in this study, the authors controlled for many confounding maternal and infant factors, but they were unable to include antenatal steroid administration in the analysis.

A clearer understanding of this association between mode and timing of infant delivery is needed because this may affect overall neonatal morbidity and mortality and guide decision-making when determining delivery method. Until these matters are further settled through future study, the decision on method and timing of delivery to reduce the risk of IVH cannot be based upon these factors alone.

### ADDITIONAL MATERNAL CONSIDERATIONS

The role of maternal health conditions, including inflammatory processes, placental abruption, preeclampsia, obesity, smoking, and administration of intrapartum medications (eg, tocolytics, nonsteroidal anti-inflammatory drugs, phenobarbital, vitamin K) on GMH-IVH have all been studied. The presence of chorioamnionitis appears to be an independent risk factor for the development of any grade IVH, (24)(25) whereas preeclampsia may provide some degree of protection against the development of severe IVH. (26)(27) In the EPIPAGE2 study, placental abruption was found to be an independent risk factor for severe IVH and, in the setting of a maternal inflammatory state, it also further increased IVH risk. (28) Although a host of maternal medications have been studied, only antenatal steroids, antibiotics in the settings of chorioamnionitis, and possibly maternal tocolytics during preterm labor, specifically nifedipine or atosiban, have been shown to reduce IVH. (29) More investigation is needed to further clarify and understand the impact of maternal health conditions and medications on GMH-IVH. Continued discovery of the maternal processes involved and their fetal effects may help reduce



and potentially even prevent GMH-IVH in the preterm population.

## DELAYED CORD CLAMPING

Delayed cord clamping (DCC) has been recommended by ACOG and American Academy of Pediatrics for 30 to 60 seconds in vigorous term and preterm infants. (30) Placental transfusion during DCC can provide up to 80 mL of blood in a term infant in 1 minute and up to 40 to 50 mg/kg of iron, immunoglobulins, and stem cells. In multiple studies, DCC has been shown to decrease the incidence of all grades of IVH, but did not show any benefit in severe IVH. (31) However, because of the delay in resuscitation, DCC is not recommended when the infant is not vigorous, even though these neonates may benefit from placental transfusion. Umbilical cord milking (UCM), in which blood is stripped from an unclamped umbilical cord 2 to 3 times before clamping, can shorten the time to resuscitation. A meta-analysis of 7 randomized controlled trials of UCM versus control intervention of DCC or immediate cord clamping (ICC) in infants of less than 33 weeks' gestation showed reduced risk of all grades of IVH but not severe IVH. (32) Studies comparing UCM with ICC in preterm infants of less than 28 and 32 weeks of gestation, respectively, also showed a significant decreased incidence of all grades of IVH but not severe IVH. (33)(34)

DCC after cesarean delivery has been shown to have a lack of adequate placental transfusion with nonsignificant increases in blood volumes after DCC compared with early cord clamping. (35) Most studies on DCC do not stratify based on mode of delivery. A randomized controlled trial comparing UCM with DCC in preterm infants of less than 32 weeks' gestation delivered via CS showed higher hemoglobin and blood pressure over the first 15 hours after birth but was not powered to assess difference in IVH. (36)

Although UCM is not routinely recommended, studies demonstrate that UCM is better than ICC when DCC cannot be performed and may be more beneficial than DCC in CS deliveries. Larger clinical trials on DCC, DCC with ventilation, and UCM (NCT02996799, VentFirst NCT02742452, PREMOD2 NCT03019367, NCT03200301) are ongoing and will hopefully further clarify this matter.

## HYPOTHERMIA

The ideal neonatal body temperature lies between 97.7°F (36.5°C) and 99.5°F (37.5°C), with mild hypothermia defined as 96.8°F (36.0°C) to 97.5°F (36.4°C), moderate

hypothermia ranging between 91.2°F (32.9°C) and 96.6°F (35.9°C), and severe hypothermia at less than 89.6°F (32°C). (37) In the delivery room, newborns experience evaporative, radiant, convective, and conductive heat loss. Preterm infants are at higher risk for neonatal hypothermia, with birthweight being the most significant determining predictor of admission hypothermia in VLBW infants. (38) A cohort study of VLBW infants showed no increased risk for severe IVH with mild hypothermia, but higher odds of severe IVH with moderate hypothermia. (39) Given the need to maintain normothermia, the Neonatal Resuscitation Program recommends that for preterm newborns, the delivery room temperature should be set to 73.4°F (23°C) to 77°F (25°C), and for newborns of less than 32 weeks' gestation, a plastic wrap/bag, thermal mattress, and hat should be used to reduce heat loss. (40)

## OXYGENATION

Preductal oxygen saturation (SpO<sub>2</sub>) monitoring is standard in delivery room resuscitation and oxygen is titrated to goal SpO<sub>2</sub> levels based on full-term infants. According to current recommendations, preterm resuscitation should be initiated with low fraction of inspired oxygen (Fio<sub>2</sub>), beginning with Fio<sub>2</sub> of 0.21 to 0.3. (40) Meta-analysis of 8 randomized controlled trials comparing resuscitation with low (Fio<sub>2</sub> <0.3) versus high (Fio<sub>2</sub> >0.6) oxygen in preterm infants of less than 28 weeks' gestation found no difference in overall risk of death or other preterm morbidities including IVH greater than or equal to grade 2. (41) However, infants requiring resuscitation initiated with low oxygen were less likely to reach a goal 5-minute SpO<sub>2</sub> of 80% to 85%. Failing to meet this 5-minute SpO<sub>2</sub> goal was associated with an increased risk of grade 3 or higher IVH. (42) The To2rpid0 Study, an international, multicenter, randomized, unmasked study in preterm infants of less than 32 weeks' gestation was designed to determine the effect of using room air or 100% oxygen in delivery room resuscitation. The study showed a statistically significant increase in hospital mortality for infants of less than 28 weeks' gestation who received room air resuscitation. (43) These studies suggest that for preterm infants with a birth gestational age of less than 28 weeks, resuscitation should be initiated with higher oxygen than Fio<sub>2</sub> 0.21 and close attention should be paid to goal saturations for age. However, more studies are needed in preterm infants to determine optimal goal SpO<sub>2</sub> targets because current targets are based on data from full-term infants. Current clinical trials to assess oxygen parameters in delivery room resuscitation of preterm infants (HiLo NCT03825835, MONITOR NCT03256578,



STARTPreterm NCT03115463) may help guide optimal saturation goals in the delivery room.

## CEREBRAL BLOOD FLOW

Cerebral perfusion relies on cardiac output and regional vascular resistance, which is affected by autoregulatory capacities. Premature infants have diminished autoregulatory mechanisms. Changes in arterial blood pressure cause changes in cerebral blood flow. (44) Fluctuations in cerebral blood flow or obstruction of the venous system have been postulated to lead to vessel rupture in the cerebral capillary bed. (45) When possible, the factors that affect cerebral blood flow, as discussed later in this article, should be monitored in the delivery room.

Hypotension has not been consistently associated with IVH, but that may be because of differences in definitions of hypotension across studies. (46)(47) In a beagle pup model, it was shown that low blood pressure followed by a period of reperfusion or isolated hypertension alone can increase IVH. (48) However, in preterm infants, in the first 48 hours after birth, there is no positive association with blood pressure and systemic blood flow. (49) A retrospective cohort study of ELBW infants showed permissive hypotension, as defined by mean blood pressure less than gestational age but good perfusion (ie, capillary refill, heart rate, urine output, and no acidosis), had no significant increased mortality compared with normotensive patients. (50) However, the study showed a significant decrease in survival without severe neonatal complications in the hypotension group with signs of poor perfusion compared with both the normotensive and permissive hypotensive groups. This suggests that rather than blood pressure, signs of perfusion should guide treatment. (50) Therefore, delivery room goals should be to assess signs of systemic blood flow and perfusion along with blood pressure and to avoid fluctuations in blood pressure. Current clinical trials are investigating hypotension in preterm infants and effects of various treatments (HIP NCT01482559, NCT02016599, ELGANBP NCT00874393), which may help determine the best treatment goals in the delivery room.

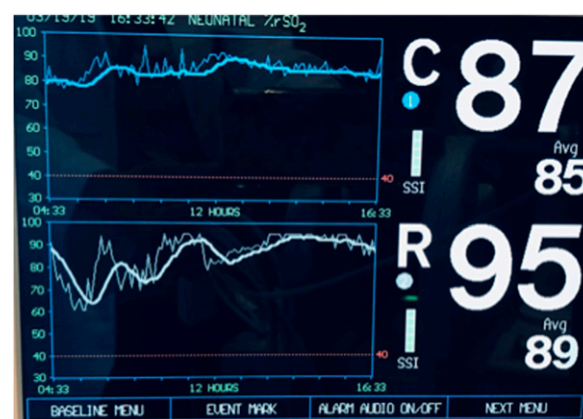
A neonate's respiratory status also affects his/her cerebral blood flow. Regional carbon dioxide ( $\text{CO}_2$ ) levels affect cerebral perfusion, such that hypercapnia results in vasodilation and increased cerebral blood flow. (44) Hypercapnia in the first 72 hours after birth is associated with severe IVH in a dose-dependent manner. (51) Bicarbonate infusions can lead to a rapid rise in  $\text{CO}_2$  levels and increase the risk of IVH. (52) Hypoxemia contributes to cerebral vasodilation and increased cerebral blood flow to maintain oxygen

delivery while hyperoxemia decreases cerebral blood flow. (44) As discussed earlier, the normal  $\text{SpO}_2$  targets for preterm infants are not well defined so hypoxemia and hyperoxemia in the delivery room are difficult to assess. The goal in the delivery room is to avoid extremes in  $\text{SpO}_2$  and  $\text{CO}_2$  levels and maintain "normal"  $\text{SpO}_2$  and  $\text{CO}_2$  levels.

It has been shown that cerebral blood flow is lower in infants who develop IVH, (18)(53) raising the possibility that monitoring cerebral blood flow may be a marker of developing IVH. Cerebral blood flow can be indirectly monitored by cerebral oximetry using near-infrared spectroscopy (NIRS) which measures the regional tissue oxygenation saturation of hemoglobin. (54)(55) Suggested goal NIRS saturation is 55% to 85% in infants and persistent values outside the range should prompt clinical assessment (Fig 2). (56) The recent Neu-Prem trial showed that it is feasible to perform NIRS in the delivery room for a preterm infant. The trial also showed that infants with severe IVH or death had lower cerebral oxygenation from 8 to 10 minutes after birth. (55) Given that cerebral blood flow plays an important role in IVH and is not well correlated with blood pressure or other standard delivery room monitoring, use of NIRS may add value. Clinical trials are under way to determine normal values, safety of NIRS, and association with IVH for neonates (NCT02147769, NCT02601339, NCT01620203, SafeBoosC NCT03770741). However, currently NIRS is not part of routine monitoring in the delivery room or the NICU.

## INTUBATION

Intubation is often accompanied by physiological responses including desaturation, bradycardia, hypotension or



**Figure 2.** Example of a near-infrared spectroscopy (NIRS) monitor screen. NIRS measures regional tissue oxygenation and is a proposed hemodynamic monitoring tool with potential use in the delivery room. NIRS probes are commonly placed on the forehead to measure cerebral saturation (C) and on the posterior flank to measure renal saturation (R). The average cerebral tissue oxygenation saturation in the figures is 85%, which is within the suggested normal range for infants.

hypertension, and increased intracranial pressures. (57) A retrospective cohort analysis of 188 VLBW infants who underwent intubation in the delivery room showed that those with no or mild IVH (grade 1 or 2) required significantly fewer intubation attempts than those with severe IVH. (57) Neonates with birthweights less than 750 g and who experienced more than 3 intubation attempts in the first 4 days after birth were 28 times more likely to develop severe IVH. (58) More studies are needed but results suggest that in the delivery room, VLBW infants should undergo intubation by an experienced caregiver.

## HEAD POSITIONING

Head positioning and effects on cerebral hemodynamics have been implicated in the development of IVH in preterm infants. Turning the head toward 1 side may functionally occlude jugular venous drainage on the ipsilateral side, causing poor venous drainage and increased intracranial pressure and blood flow. Recommendations for midline positioning with elevation of the head of the incubator has been identified as a potential practice for preventing IVH. (59) However, to date, 2 systematic reviews have showed insufficient evidence for neutral head positioning and tilt. (59)(60) No definitive recommendation on infant head positioning can be made at this time. Currently, there is a clinical trial investigating 72 hours of optimal midline positioning (NCT03543046), which may aid in clarifying recommendations for premature head positioning.

## CONCLUSION

Obstetric and pediatric specialists have made great efforts to understand the pathogenesis of GMH-IVH in preterm infants, mainly because of the associated outcomes and prognosis. Short-term IVH complications include the development of posthemorrhagic ventricular dilation. Long-term complications and prognosis are dependent on the infant's degree of prematurity, extent of hemorrhage, and presence of parenchymal involvement. A recent meta-analysis found that preterm infants with mild IVH, when compared with those without IVH, were associated with higher odds of death or moderate to severe neurodevelopmental impairment without an increase in cerebral palsy or cognitive delay at 18 to 24 months. Infants with severe IVH were at even higher odds of developing moderate to severe neurodevelopmental impairment, cerebral palsy and cognitive delay compared with those with mild IVH. (61)

The reduction in rates of severe IVH over the last few decades is likely because of advances in perinatal and

postnatal medical care and research. As we continue to define GMH-IVH risk factors and adapt our practice guidelines, we hope to see an even further reduction in the incidence of all grades of IVH and its associated short- and long-term complications.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pulmonary and non-pulmonary effects on the fetus and/or newborn infant of maternally administered steroids (including betamethasone, dexamethasone, and prednisone).
- Know the complications and effects of chorioamnionitis in the mother and the fetus.
- Know the risk factors for development, proposed mechanisms, clinical and laboratory features, and diagnosis of pediatric intraventricular hemorrhage (IVH).
- Know the proposed prevention strategies, evolution, early complications, management, and long-term consequences of pediatric IVH.
- Know the appropriate monitoring of acute and subacute pediatric IVH during the neonatal period.

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1. A male neonate born at 24 weeks' gestational age is 12 hours old and receiving mechanical ventilation. He has cardiovascular instability and has received packed red blood cell transfusion for anemia. The team is considering ultrasonography to check for intraventricular hemorrhage. With regard to the timing of ultrasonographic detection of intraventricular hemorrhage in preterm infants, what is the earliest time point at which approximately 90% of lesions are detectable?
  - A. 6 hours.
  - B. 24 hours.
  - C. 48 hours.
  - D. Day 4 after birth.
  - E. Day 14 after birth.
2. A pregnant woman who is at the 25th week of gestation presents with rupture of membranes and is in preterm labor. The health care team is considering the administration of antenatal glucocorticoids. Which of the following statements regarding this therapy is correct?
  - A. Although dexamethasone has been shown to reduce incidence of respiratory distress syndrome, it has not shown any benefit for reduction of intraventricular hemorrhage.
  - B. Although glucocorticoids do not cross the placenta, they induce maternal hormones that engage the hypothalamic-pituitary axis in the fetus, and thereby induce fetal maturity for various organ systems.
  - C. Betamethasone reduces the likelihood of intraventricular hemorrhage, but has not shown benefit in reducing respiratory distress syndrome or mortality.
  - D. Extremely low-birthweight infants exposed to antenatal dexamethasone are more likely to have neurodevelopmental and hearing impairment than infants exposed to antenatal betamethasone.
  - E. Although there are benefits of antenatal glucocorticoids, the team should wait for 1 week while tocolytic medications are administered.
3. Your team is preparing for a delivery of a neonate at 25 weeks' gestational age. Because of breech position, preeclampsia, and signs of fetal distress, a probable cesarean delivery is discussed. With regard to delivery management, which of the following strategies is appropriate?
  - A. Because of maternal health considerations, cesarean delivery is not an appropriate option before 26 weeks' gestational age.
  - B. Because of the risk of brain injury, including intraventricular hemorrhage, the latest research shows that it is appropriate to attempt passive hypothermia in the first 24 hours after birth.
  - C. Recommended treatment protocols include immediate cord clamping regardless of the patient's clinical status.
  - D. The delivery room or operating room temperature should be set to 73.4°F (23°C) to 77°F (25°C).
  - E. The preterm newborn's temperature will reflect the maternal temperature, and interventions to influence the neonatal temperature during the first hour after birth have been ineffective.

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4. A female preterm neonate born at 25 weeks' gestational age is 12 hours old. An umbilical arterial catheter provides a continuous measure of blood pressure. The blood pressure has decreased since birth and the mean arterial pressure is now 24 mm Hg. Which of the following is most concerning with regard to risk of mortality?
- A. A mean arterial blood pressure that is consistently below the gestational age at birth.
  - B. Blood pressure that is close to the median for population norms in the context of a patent ductus arteriosus.
  - C. Low blood pressure in combination with signs of poor perfusion, such as decreased capillary refill, tachycardia, and acidosis.
  - D. Systolic blood pressure that is lower than the 10th percentile for gestational age.
  - E. Urine output that is greater than 2 mL/kg per hour.
5. A male neonate born at 25 weeks' gestational age received continuous positive airway pressure since resuscitation in the delivery room and is now in the NICU. He is experiencing increased respiratory distress, repeated apnea, and increasing oxygen requirement. The team is considering intubation and giving surfactant, with subsequent plans for mechanical ventilation. Which of the following statements is correct regarding prevention of intraventricular hemorrhage for this patient?
- A. After intubation and stabilization on the ventilator, the optimal position for the neonate's head will be tilted 30 degrees to one side, with switching to the alternate side every 6 to 12 hours.
  - B. Both hypoxemia and hyperoxemia lead to cerebral vasodilation and increased cerebral blood flow.
  - C. Hypercapnia in the first 72 hours after birth is associated with severe intraventricular hemorrhage in a dose-dependent manner.
  - D. Prophylactic infusion of sodium bicarbonate over the first 24 hours to prevent acidosis has been associated with decreased incidence of both any and severe intraventricular hemorrhage.
  - E. The number of intubation attempts has not been shown to correlate with intraventricular hemorrhage risk.



# Reducing Germinal Matrix-Intraventricular Hemorrhage: Perinatal and Delivery Room Factors

Jina Lim and Eunice Hagen

*NeoReviews* 2019;20:e452

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# Index of Suspicion in the Nursery

## 1 Severe Jaundice in a 2-day-old Term Neonate

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### PRESENTATION

A 2-day-old, 2.68-kg term male neonate is brought to the emergency department with lethargy, poor feeding, and significant generalized jaundice. He was born via spontaneous vaginal delivery at home to a gravida 4, para 3 Amish woman under the supervision of a midwife, at an estimated gestational age of 39 weeks after an uncomplicated pregnancy with scant prenatal care. Jaundice was noticed 7 hours after birth. The neonate has only breastfed 5 to 6 times since birth, and passed a normal-colored stool at home. Prenatal laboratory findings are unavailable because of limited prenatal care. The mother's blood type is AB, Rh negative. The mother's obstetric history includes a previous miscarriage (4 years earlier), a previous stillbirth at 30 weeks' gestation (3 years earlier), and a term pregnancy (2 years earlier). She had received Rh<sub>o</sub>(D) immune globulin 3 weeks after the miscarriage, 2 weeks after the stillbirth delivery, and 2 weeks after the most recent pregnancy. The mother, father, and 2-year-old brother are reportedly healthy.

Review of systems at admission is significant for decreased activity, poor feeding, and generalized, intense yellow discoloration of the skin. The infant has no fever, vomiting, diarrhea, constipation, bloody stools, seizures, or hypertonia. Physical examination reveals a weak cry, lethargy, scleral icterus, soft liver edge 3 cm below the right costal margin, and significant generalized jaundice of the entire body. No dysmorphic features are appreciated.

### CASE PROGRESSION

Initial evaluation revealed a total serum bilirubin (TB) of 49.4 mg/dL (845  $\mu$ mol/L), conjugated bilirubin of 42 mg/dL (718  $\mu$ mol/L), unconjugated bilirubin of 10.7 mg/dL (183  $\mu$ mol/L), reticulocyte count greater than 23, and hemoglobin of 12.6 g/dL (126 g/L). Urinalysis demonstrated dark brown urine. Serum aspartate aminotransferase (AST) was elevated at 239 U/L (4  $\mu$ kat/L), serum alanine aminotransferase (ALT) was elevated at 55 U/L (0.9  $\mu$ kat/L), serum alkaline phosphatase was 186 U/L (3.1  $\mu$ kat/L), and partial thromboplastin time was elevated at 30.7 seconds. Urine culture revealed *Escherichia coli* at 10,000 to 100,000 colony-forming units. Peripheral smear demonstrated mild anemia with marked reticulocytosis and numerous immature erythroids. The neonate's blood type was B, Rh positive. Direct Coombs test result was 4+, indicating antibody-mediated hemolysis in the newborn. A jaundice chip, which targets 5 genes (*ABCB11*, *ABCB4*, *ATP8B1*, *JAG1*, and *TJP2*), was drawn (the negative result was not received until later, ruling out Alagille syndrome and progressive familial intrahepatic cholestasis as possible causes). Endocrinopathies (hypothyroidism

**NOTE** The editors and staff of NeoReviews find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in NeoReviews when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

**AUTHOR DISCLOSURE** Drs Lyle and Turcu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Turcu's current affiliation is Department of Pediatrics, Division of Newborn Medicine, Tufts Medical Center, Boston, MA.

and hypopituitarism) were excluded (normal thyroid-stimulating hormone and free thyroxine). Newborn screening results were normal. Abdominal ultrasonography showed a normal-appearing liver and gallbladder, no biliary ductal dilation, and patent vessels.

The 2004 American Academy of Pediatrics guidelines for treatment of hyperbilirubinemia state that, “In unusual situations in which the direct bilirubin level is 50% or more of the TB, there are no good data to provide guidance for therapy.”<sup>(1)</sup> Treatment included intensive phototherapy, intravenous fluids, double volume exchange transfusion, intravenous immunoglobulin, ampicillin, cefotaxime, acyclovir, and phenobarbital (for activation of the promoter sequence of hepatic UGT1A1). The Fig demonstrates the decline of bilirubin after each of these interventions. Enteral feeds were initiated after 2 days of hospitalization, which the infant tolerated well.

At discharge on hospital day 7, laboratory findings were as follows: TB 9.3 mg/dL (159  $\mu$ mol/L), conjugated bilirubin 4.5 mg/dL (77  $\mu$ mol/L), unconjugated bilirubin 2.5 mg/dL (42.8  $\mu$ mol/L), AST 81 U/L (1.3  $\mu$ kat/L), ALT 36 U/L (0.6  $\mu$ kat/L), and alkaline phosphatase 82 U/L (1.4  $\mu$ kat/L). Hepatobiliary iminodiacetic acid scan was offered, but the parents declined because of the normal hepatic ultrasound scan with decreasing bilirubin levels. They also declined brain magnetic resonance imaging because the neurologic findings at discharge were reassuring.

## FOLLOW-UP

The infant was evaluated in the developmental pediatrics clinic at 2 months, 19 days of age. Growth was appropriate: weight 5.88 kg (36th percentile), length 59.7cm (35th percentile), and head circumference 38.5cm (9th percentile). Jaundice had resolved. TB concentration was 0.8 mg/dL (13.7  $\mu$ mol/L) and direct bilirubin 0.0 mg/dL (0.0  $\mu$ mol/L). He appeared developmentally appropriate with normal findings on neurologic examination. He continues to be followed closely.

## DISCUSSION

Jaundice in the first few days after birth is a common neonatal problem, occurring in approximately two-thirds of newborns. (2) Most cases are represented by unconjugated hyperbilirubinemia, which is usually treated with phototherapy. Conjugated hyperbilirubinemia is much less common in the neonatal period, and is indicative of cholestasis. Neonatal jaundice caused by unconjugated versus conjugated hyperbilirubinemia cannot be differentiated with physical examination alone. Direct bilirubin concentration greater than 1.0 mg/dL (17.1  $\mu$ mol/L) with TB less than 5 mg/dL (85.5  $\mu$ mol/L), or a direct bilirubin greater than 20% of the TB (if TB >5 mg/dL) is diagnostic of conjugated hyperbilirubinemia. Conjugated hyperbilirubinemia and cholestasis can have infectious, metabolic, or

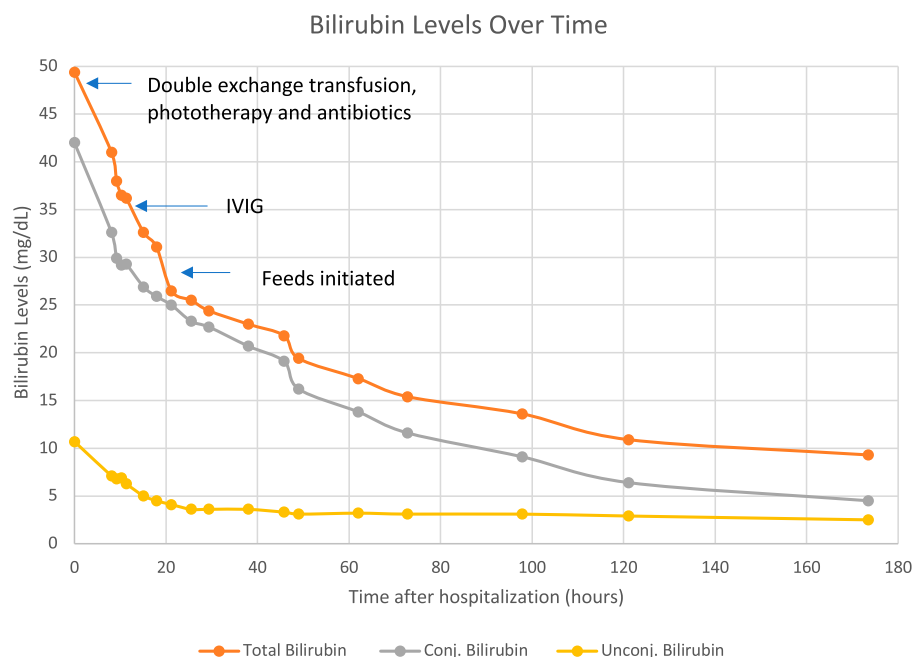


Figure. Bilirubin levels over time.

obstructive causes, and is the most common marker of cholestasis. (3)(4)(5)(6)(7) Common causes of obstructive cholestasis include biliary atresia, choledochal cysts, bile duct paucity, neonatal sclerosing cholangitis, inspissated bile syndrome, gallstones/biliary sludge, cystic fibrosis, and Caroli disease. (2)(7)(8)

The current patient was born full term, had inadequate prenatal care, and demonstrated significant generalized jaundice within the first 7 hours after birth. He presented with hemolytic anemia (likely because of Rh incompatibility) and conjugated hyperbilirubinemia (which was unusual given that Rh incompatibility usually results in unconjugated hyperbilirubinemia). The most common causes of cholestasis had been excluded: Alagille syndrome and progressive familial intrahepatic cholestasis (negative jaundice chip), hypothyroidism and hypopituitarism (normal thyroid-stimulating hormone and free thyroxine), congenital heart disease (normal chest radiograph and a patent foramen ovale on echocardiography). Urinary tract infection with *E coli* could have been a contributory factor, but it is an unlikely main cause. In cases of suspected cholestasis, ultrasonography is the initial imaging modality of choice. (9) After all test results returned, the exclusion diagnosis in this case remained Rh incompatibility with severe chronic hemolysis, complicated by inspissated bile syndrome.

Inspissated bile syndrome is a rare clinical entity, with an incidence of 1 in 175,000 live births as reported in England. (9)(10) The medical literature reveals a paucity of neonatal inspissated bile syndrome cases; the few cases reported are in the setting of cystic fibrosis or metabolic disorders, (6)(11) ABO incompatibility after transfusion, (12) or drug-induced. (13) In these cases, the infant was older at the time of presentation, and TB and conjugated bilirubin levels were well below the values recorded for our patient.

### Lessons for the Clinician

- Two-thirds of newborns will experience jaundice within the first few days after birth.
- Conjugated hyperbilirubinemia is less common than unconjugated hyperbilirubinemia and is indicative of cholestasis caused by infection, metabolism defects, or obstruction.
- Common causes of obstructive cholestasis include biliary atresia, choledochal cysts, bile duct paucity, neonatal sclerosing cholangitis, inspissated bile syndrome, gallstones/biliary sludge, cystic fibrosis, and Caroli disease.
- Evaluation for neonatal cholestasis includes blood, urine, and cerebrospinal fluid cultures, urinalysis, cerebrospinal fluid studies, complete blood cell count with differential, comprehensive metabolic panel, prothrombin

time/international normalized ratio, and partial thromboplastin time. Newborn screening results should be reviewed for possible metabolic causes. Abdominal ultrasonography should be performed to assess for biliary atresia. A jaundice chip is useful if Alagille syndrome or progressive familial intrahepatic cholestasis is suspected.

Note: This case is based on a presentation by Drs Lyle and Turcu at the Joint Plenary Poster Session of the Southern Regional Meeting of American Federation for Medical Research, New Orleans, LA, on February 22, 2018 (Poster No. 303).

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the factors, including red cell life span, enzyme defects, and red cell structural abnormalities, associated with an increase in bilirubin production.
- Know the factors associated with a decrease in neonatal serum bilirubin excretion, including those that affect the enterohepatic circulation of bilirubin.
- Know bilirubin physiology, including pathways of synthesis, transport, and metabolism, in the fetus and neonate.

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## Case 1: Severe Jaundice in a 2-day-old Term Neonate

Allison Lyle and Rodica Turcu

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# Index of Suspicion in the Nursery

## 2 Soft Tissue Congenital Neck Mass

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*\*Department of Neonatology and Pediatrics, and <sup>†</sup>Department of Hematology/Oncology and Pediatrics, University of New Mexico, Albuquerque, NM*

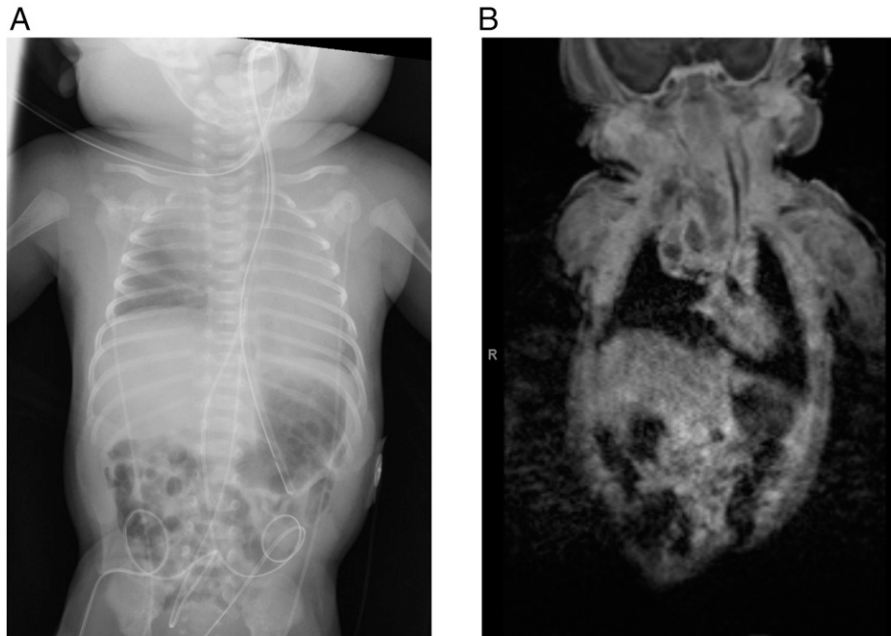
### PRESENTATION

A female infant at 35 weeks and 4 days of gestation is born at a community hospital to a 25-year-old primigravida woman via emergency cesarean section because of fetal distress. Prenatal care had been good, and unexplained polyhydramnios had been noted during an otherwise uncomplicated pregnancy. The infant requires full cardiopulmonary resuscitation. Apgar scores are 0, 2, and 3 at 1, 5, and 10 minutes, respectively. At delivery, it is noted that she has a right neck mass, and she remains intubated for airway protection. The infant is transferred to another facility where she receives therapeutic hypothermia for 72 hours before being transferred to the tertiary care center for further evaluation of the mass and airway. On admission, she is noted to have superior vena cava syndrome with facial plethora. Radiography shows deviation of her airway to the left (Fig 1A). Computed tomography (CT) and magnetic resonance imaging (MRI) reveal a 5.2×3.6×2.4-cm multiloculated cystic, heterogeneous, septated mass with multiple fluid levels displacing mediastinal structures and compressing the right internal jugular vein, right internal carotid artery, right subclavian artery and vein, right vertebral artery, and the trachea (Fig 1B); it extends from the level of the inferior thyroid gland into the superior mediastinum.

The next day, day 6 after birth, an open excisional biopsy and fine needle aspiration is performed to evaluate for any pathology. Because of her worsening clinical status, the patient is taken to the operating room on day 10 after birth for excision of the mass. The mass is found to be adherent to the posterior mediastinum, extending through the chest into the neck, abutting and adherent to the trachea, extending over the anterior part of the esophagus, and adherent to the spine. No residual mass was left in the chest, but 2 areas of residual mass were left near the trachea and brachial plexus. The patient's superior vena cava syndrome improves dramatically and her clinical status stabilizes. Ten days later, she undergoes successful extubation. Micro-laryngoscopy and bronchoscopy confirm no airway narrowing at the time of extubation.

Pathology reveals fibrous histiocytic tumor, most likely juvenile xanthogranuloma (JXG). Pediatric oncology recommends chemotherapy with clofarabine, which is started in the NICU. She is transferred after 2 rounds of clofarabine to the oncology service. She undergoes plication of the right hemidiaphragm 2 months after extubation because of continued respiratory distress, likely secondary to diaphragmatic eventration; she is able to wean slightly on respiratory support, but remains hospitalized requiring high flow. One week later, radiography shows a stable opacity of unclear etiology (true soft tissue mass vs small-volume pleural fluid) in the region of the right upper lobe without mediastinal shift (Fig 2A). Two

**AUTHOR DISCLOSURE** Drs Patel, Mayfield, and Stefanescu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



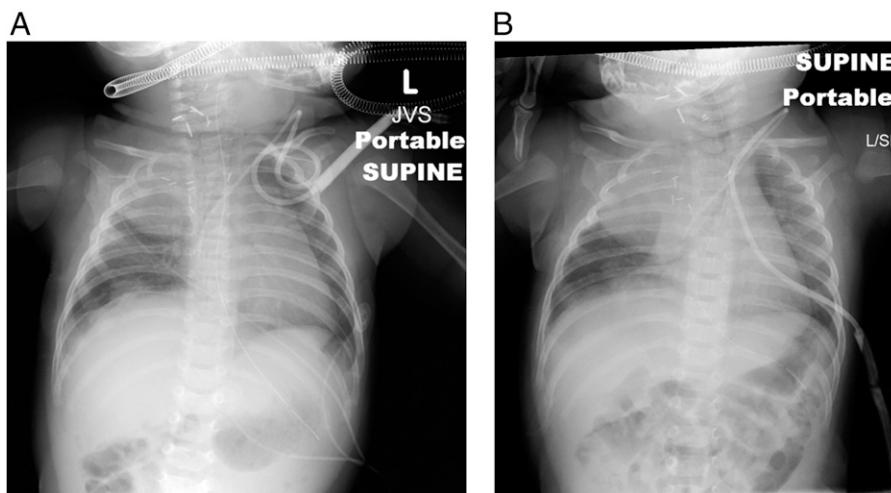
**Figure 1.** A. Radiograph showing deviation of the trachea and esophagus to the left. Soft tissue mass is also visible over the right upper lung fields. Right and left diaphragms are uneven. B. Coronal MRI showing a multiloculated cystic and septated mass with multiple fluid levels resulting in deviation of mediastinal structures.

weeks later, because of worsening respiratory distress, another radiograph is obtained, which reveals a right lung opacity with left shift of the mediastinum (Fig 2B). The patient had received her third round of clofarabine in the interim between Figs 2A and 2B. An urgent CT shows recurrence of the mass with extension into the spinal column and deviation of the spinal cord, trachea, and esophagus (Fig 3A-D). The mass measures  $5.8 \times 4.8 \times 4.3$  cm in the cervical region, larger than the original mass. The patient is intubated and emergently transferred to another center with

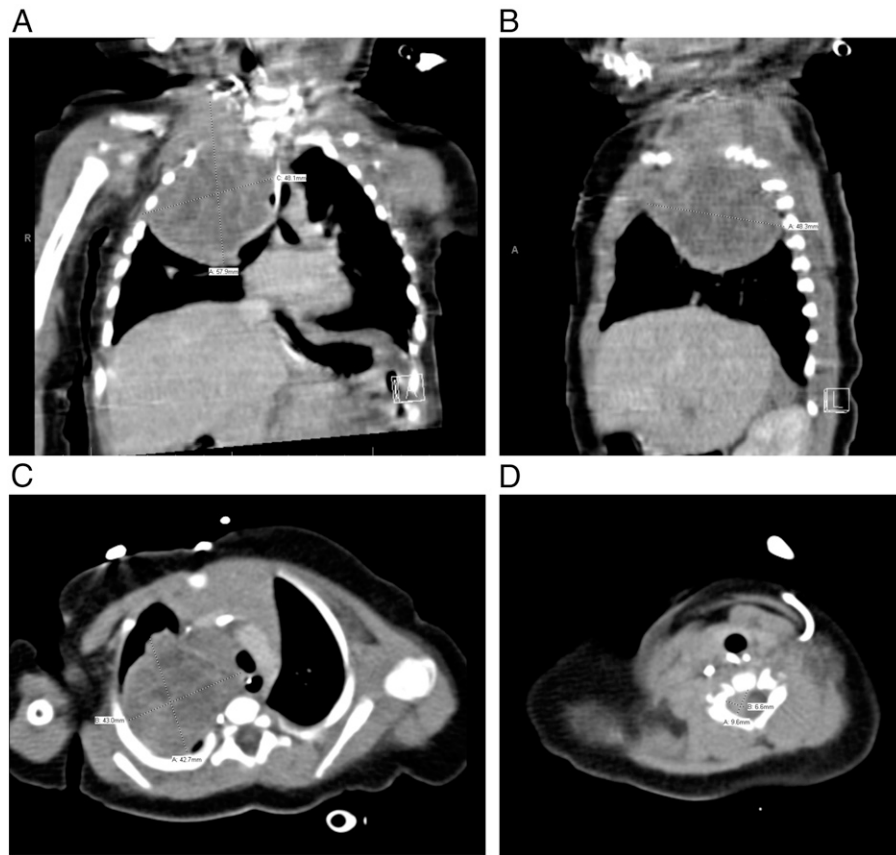
pediatric neurosurgery. She subsequently dies during surgery because of hemorrhage.

## DISCUSSION

JXG is a rare nonmalignant histiocytic tumor of dendritic cell origin with onset most often in infancy. Lesions may be present at birth. The incidence is estimated at 1 in 1 million children. (1) It is most often found as a solitary cutaneous skin nodule of the head and neck region, with other



**Figure 2.** A. Radiograph after 2 courses of clofarabine shows a stable right upper lobe opacity of unclear etiology without mediastinal shift. B. Two weeks later, radiograph after a third course of clofarabine shows enlargement of the right upper lobe opacity with mediastinal shift.



**Figure 3.** A. Coronal CT showing large heterogenous mass occupying the right upper thorax and extending into the neck. B. Sagittal CT showing the anterior-posterior dimension of the mass. C. Axial CT showing deviation of the mediastinal structures. D. Axial CT showing extension of the mass into the spinal column with deviation of the spinal cord.

common locations including the trunk and extremities. Other manifestations of JXG include systemic disease, solitary subcutaneous mass, multiple cutaneous lesions, and deep soft tissue mass. (2) The diagnosis of systemic disease requires the involvement of at least 2 visceral organs, with the central nervous system and liver being the most common sites. (3) JXG often regresses spontaneously within 1 year of presentation, and observation is the recommended treatment in most cases. If intervention is needed, the treatment is often steroids. However, when the mass causes clinical compromise, resection is recommended. After resection, even if residual tumor remains, JXG often regresses spontaneously. Chemotherapy is not recommended except in the case of nonresectable tumors in patients with clinical compromise, or in patients with systemic disease and vital organ involvement. Chemotherapy with Langerhans cell histiocytosis (LCH) treatment regimens, such as prednisone and vinblastine, or with medications such as clofarabine and cladribine, has been used. (1)(4)(5)

The differential for fibrohistiocytic tumors includes angiomatoid fibrous histiocytoma, LCH, and other non-LCH

tumors such as Erdheim-Chester disease and Rosai-Dorfman disease. (3) Immunohistochemistry is important in differentiating these tumors, but is not diagnostic. In JXG, mononuclear and spindle cells are often immunoreactive for CD68, CD14, CD163, and factor XIIIa, and nonreactive for CD1a and S100 protein. (1)(2)(3) For angiomatoid fibrous histiocytoma, cells are immunoreactive for vimentin, epithelial membrane antigen, desmin, and CD68 and negative for S100 protein. (6) For LCH, diagnosis is supported by the presence of S100 protein and CD1a, which helps distinguish LCH from JXG. (3) In the current patient, pathologic findings included immunoreactivity toward CD68, CD163, and factor XIIIa, and nonreactivity to CD1a, S100 protein, epithelial membrane antigen, and desmin, among a number of other factors, which is most consistent with JXG. Touton giant cells, which are usually present in the classic form of JXG, (1)(2)(3) were not noted in the current case.

This case is unique because the deep soft tissue JXG rapidly increased in size and invaded the spinal column, causing clinical compromise despite resection and ongoing

treatment with clofarabine. Barroca et al report a similar case of a cervical JXG that recurred after resection. (7) Histopathology was similar and Touton giant cells were not present. However, the recurrence was less severe and the patient was not receiving medication at the time of recurrence. The patient in that report had another resection, after which there was no further recurrence. To our knowledge, there are no other case reports of a deep soft tissue JXG with aggressive recurrence.

### Lessons for the Clinician

- Fibrohistiocytic tumors should be included in the differential diagnosis of deep soft tissue masses. Juvenile xanthogranuloma is the most common fibrohistiocytic tumor.
- Juvenile xanthogranuloma may present without skin lesions.
- Most juvenile xanthogranulomas regress spontaneously. Treatment may be needed in cases of clinical compromise, and can include resection, steroids, or chemotherapy.
- The absence of CD1a and S100 protein on immunohistochemistry can help exclude Langerhans cell histiocytosis.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Recognize the imaging features of extrapulmonary causes of respiratory distress.

- Know the clinical features of an infant with airway obstruction.
- Know the clinical manifestations and approaches to therapy of neck masses in the newborn infant.

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**Case 2: Soft Tissue Congenital Neck Mass**  
Sonal N. Patel, Jodi R. Mayfield and Beatrice M. Stefanescu  
*NeoReviews* 2019;20:e468  
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# Index of Suspicion in the Nursery

## 3 An Unusual Case of Transient Neonatal Encephalopathy

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### PRESENTATION

A 7-day-old female neonate presents to a local hospital with lethargy, grunting, fast breathing, and abnormal movements after a short history of poor feeding overnight. She was born at 39 weeks' gestation via cesarean section with a birthweight of 3,100 g to a 34-year-old woman. The parents are nonconsanguineous and the pregnancy was a result of in vitro fertilization with their own gametes. Antenatal screening and scans were normal. Cesarean section was performed because the labor did not progress; the neonate did not need any resuscitation. She nursed with the mother and went home breastfeeding on day 3 after birth. There is no family history of early neonatal deaths or neurologic dysfunction.

The neonate is brought to our tertiary neonatal center after stabilization with fluid bolus, broad-spectrum antibiotics, levetiracetam for suspected seizures, and mechanical ventilation. Initial differential diagnosis includes late-onset sepsis with meningitis and inborn error of metabolism with encephalopathy. Examination shows no dysmorphic features or neurocutaneous markers, and the head circumference is 32.6 cm. The infant is stuporous with paucity of spontaneous movements, depressed neonatal reflexes, and hypotonia. She is well perfused with normal heart sounds and femoral pulses and has no oxygen requirement. There is no pallor or jaundice and there is no organomegaly.

Arterial blood gas shows severe metabolic acidosis with pH of 7.15,  $P_{CO_2}$  21 mm Hg (2.8 KPa), and bicarbonate 7.1 mEq/L (7.1 mmol/L). Normoglycemia is noted, with ongoing glucose infusion. Initial metabolic evaluation reveals hyperammonemia of 476  $\mu$ g/dL (340  $\mu$ mol/L) with mildly raised lactate at 36 mg/dL (4 mmol/L). Infection markers, blood counts, liver function tests, electrolytes, and creatinine concentration are within normal range. Enteral feeds are withheld, measures are taken to lower ammonia and prevent catabolism with oral sodium benzoate, parenteral nutrition with glucose infusion rate of 8 mg/kg per minute, and protein infusion of 0.25g/kg per day. Serial ammonia levels decline (at 4, 10, and 24 hours after admission, it is 434  $\mu$ g/dL [310  $\mu$ mol/L], 336  $\mu$ g/dL [240  $\mu$ mol/L], and 231  $\mu$ g/dL [165  $\mu$ mol/L], respectively) and normalize completely by 72 hours of admission. Brain ultrasonography shows cerebral edema and electroencephalography on day 2 of admission shows frontocentral and temporal epileptogenicity with normal background. Extended metabolic evaluation using tandem mass spectroscopy shows normal levels of plasma amino acids, acyl carnitine levels, and slightly low carnitine levels, making the diagnosis of organic acidemia, urea cycle defects, and defects

**AUTHOR DISCLOSURES** Drs Kumar, Athreya, Achuta, and Sundarraju have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

in fatty oxidation pathways less likely. Cerebrospinal fluid shows normal cell counts, biochemical profile, and lactate levels. Ammonia levels normalize, metabolic derangement resolves, and the infant's neurologic status returns to normal by day 7 of admission. She is taken off respiratory support. Gradual introduction of enteral feeds with breast milk does not result in any neurologic deterioration or rise in ammonia levels. Further evaluation shows normal urine orotic acid and cerebrospinal fluid  $\alpha$ -amino adipic semialdehyde levels. Magnetic resonance imaging and magnetic resonance spectroscopy findings were normal, apart from a small infarct in the right caudothalamic groove. She has no clinical seizures but repeat electroencephalography a week later still shows some epileptogenicity and phenobarbital is added.

She is discharged from the hospital 2 weeks after admission. Because she presented in a metabolic crisis with transient hyperammonemia and encephalopathy with no diagnosis forthcoming from metabolic evaluation and brain imaging, genetic testing is carried out. Focused exome sequencing shows homozygous missense variant in carbonic anhydrase 5A (CA-VA) gene which is likely to be a pathogenic variant. Repeat carnitine measurements are normal. On follow-up she is thriving, remains neurologically normal, and is achieving her developmental milestones; her antiepileptic medications are being tapered.

## DISCUSSION

Neonatal encephalopathy results from a wide variety of causes, among which hyperammonemia causing neonatal encephalopathy is considered to be an emergency requiring early identification and initiation of therapy. (1) Reaching an accurate diagnosis for the cause of hyperammonemia is often challenging and requires extensive investigation; often, even after extensive evaluation, the diagnosis may not be reached. Reversible conversion of carbon dioxide to bicarbonate is catalyzed by carbonic anhydrase (CA). Mitochondria are impermeable to bicarbonate, and 2 intramitochondrial carbonic anhydrases CA-VA and CA-VB are important in providing bicarbonate for multiple mitochondrial enzymes that catalyze the formation of essential metabolites of intermediary metabolism in the urea and Krebs cycles. (2)(3) CA-VA deficiency is an autosomal recessive inborn error of metabolism characterized clinically by acute onset of encephalopathy in infancy or early childhood. Biochemical evaluation shows multiple metabolic abnormalities, including metabolic acidosis and respiratory alkalosis. Other abnormalities

include hyperammonemia, hypoglycemia, increased serum lactate and alanine, and evidence of impaired provision of bicarbonate to essential mitochondrial enzymes. (4) Apart from episodic acute events in early childhood, the disorder shows a relatively benign course. Treatment with dextrose, bicarbonate, and carnitine provides clinical stability. Individuals may develop episodic acute metabolic decompensation during intercurrent illnesses. (4) CA-VA deficiency and long-term follow-up data have been sparsely reported in literature. Van Karnebeek et al reported 3 cases in 2 unrelated families. In 1 family, an affected girl showed mild axial hypotonia with average development, with below-average motor coordination at age 4.5 years, whereas her brother showed below-average psychomotor development at age 2.3 years. The third child showed normal psychomotor development at age 6 months. Diez-Fernandez et al described 10 more patients with CA-VA deficiency who were identified among a group of 96 patients with unexplained hyperammonemia, suggesting that this disease may be more common than rare forms of urea cycle disease such as N-acetylglutamate synthase deficiency. (5)

## Lessons for the Clinician

- Neonatal encephalopathy with hyperammonemia warrants emergent treatment and efforts to establish underlying diagnosis.
- CA-VA deficiency is a differential diagnosis of early-onset life-threatening metabolic crisis, with hyperammonemia, hyperlactatemia, and ketonuria. This can be identified with focused exome sequencing and may be a more common cause of hyperammonemia than some rare metabolic errors. (5)
- CA-VA mutation will enable formulating sick day plans, genetic counseling, and screening of family members.
- Although metabolic derangement and encephalopathy may be transient, long-term neurodevelopment follow-up is indicated.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes, clinical features, laboratory evaluation, and acute management of metabolic encephalopathies in newborn infants

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## Pseudosinusoidal Pattern in Labor

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min

**AUTHOR DISCLOSURE** Dr Demasio has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. **Arterial Umbilical Cord Gas Values**

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:  
Absent: Amplitude range is undetectable  
Minimal: Amplitude range is greater than undetectable to 5 beats/min  
Moderate: Amplitude range is 6–25 beats/min  
Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

#### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## THE CASE

A 23-year-old gravida 2, para 0-0-1-0 woman arrived at the labor and delivery (L&D) department for a scheduled late-term induction of labor at 40 5/7 weeks of gestation. She received routine prenatal care for her pregnancy from the first trimester, and her aneuploid screening at 12 2/7 weeks of gestation found her to be at “low risk.” Third-trimester ultrasound examination revealed an estimated fetal weight at the 43rd percentile for gestational age. Her prenatal course was uncomplicated and her medical/surgical history was negative. She denied the use of tobacco products or

illicit drugs, and her only medication was prenatal vitamins. Laboratory values were all normal, and a third-trimester group B *Streptococcus* culture was negative. Blood pressure readings throughout her prenatal visits were within normal limits, but on the day of arrival at L&D, her blood pressure was mildly elevated to 130/92 mm Hg. Her complete blood cell count, urine tests, and chemistry laboratory tests were rechecked in L&D and found to be within normal limits. The FHR tracing was category 1 as shown in Fig 1.

Induction of labor was started with misoprostol for cervical ripening. Examination of the cervix revealed it permitted a fingertip, but was long and uneffaced, and the fetal station was high. Epidural analgesia was placed 5 hours after the start of induction, and the FHR tracing changed to a category 2 tracing because of minimal variability (Fig 2). Over the next hour, the cervix was 1-cm dilated, 50% effaced and –1 station, so oxytocin was initiated. After another 5 hours, an intracervical Foley catheter was placed for mechanical dilation. The FHR tracing developed a pseudosinusoidal pattern (Fig 3) that continued for more than 10 hours. The intracervical Foley was eventually expelled and the cervix was 5-cm dilated, 75% effaced, and +1 station. Twenty-four hours after the start of labor induction, membranes were artificially ruptured and clear amniotic fluid was noted. The FHR tracing after the rupture of membranes had minimal variability (Fig 4), and contractions showed a tachysystole pattern. The cervix remained unchanged after another 4 hours and an intrauterine pressure catheter was placed. The FHR tracing again revealed a pseudosinusoidal pattern (Fig 5), with a regular contraction pattern. The cervix did not change for the next 10 hours and a cesarean delivery was proposed to the woman, after a total of 34 hours, for failed induction of labor. She accepted the procedure and the FHR tracing within 1 hour of delivery was category 1 (Fig 6).

A male infant was delivered via primary cesarean section with a birthweight of 3,475 g. Apgar scores were 1, 3, and 3 at 1, 5, and 10 minutes, respectively, which was unexpectedly low for the FHR tracing shown in Fig 6 before the delivery. The neonate underwent intubation in the operating room and was transferred to the NICU. The umbilical cord gases (Table 2) represented a mild respiratory acidosis. The infant was evaluated for therapeutic hypothermia, but did not meet the criteria, and after 2 hours, the infant’s tone and respirations improved and he underwent successful extubation. His quick recovery was thought to be reflective of clearance of the epidural medication. Cultures sent to evaluate for infection were negative, and his brain magnetic resonance

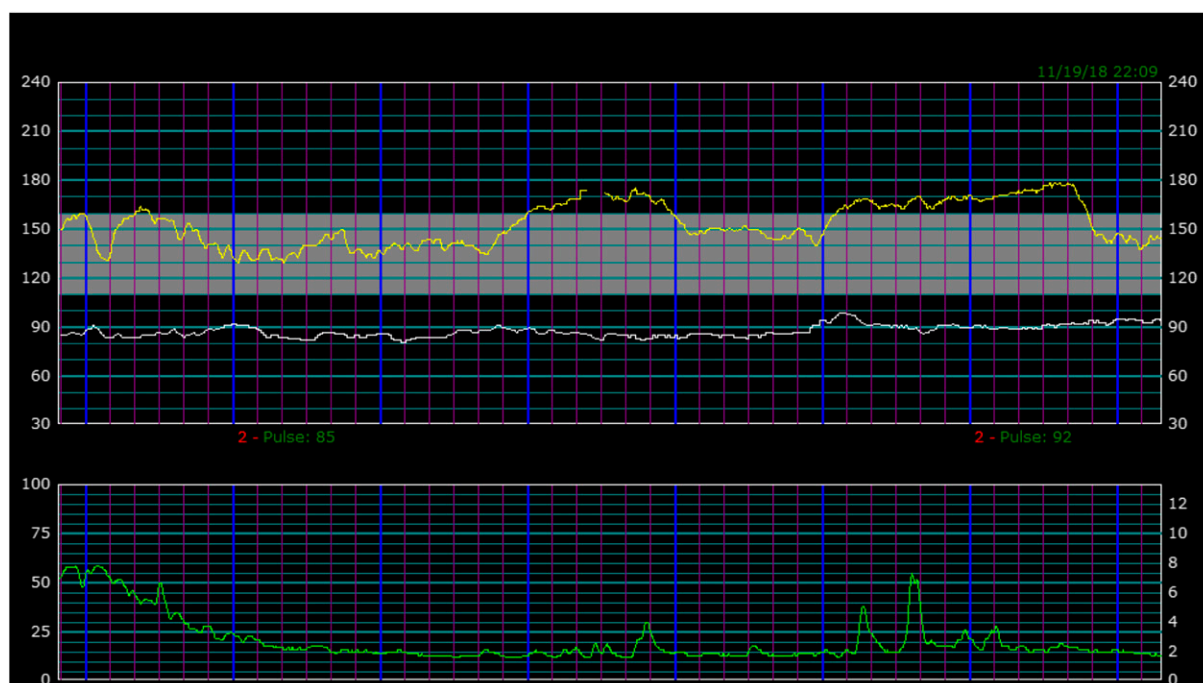


Figure 1. Electronic fetal monitoring strip 1.

imaging scan was normal. The infant was discharged from the hospital after 5 days with appropriate medical follow-up.

## DISCUSSION

Labor induction leads to successful vaginal delivery in approximately 75% of cases, and avoids the risks associated

with postterm pregnancies, such as meconium aspiration syndrome and stillbirth. The risks of labor induction in low-risk gestations must be balanced with its benefits. Pregnancies that may otherwise enter into spontaneous labor if given more time must be differentiated from those that might suffer the consequences of postterm gestations at 42 weeks

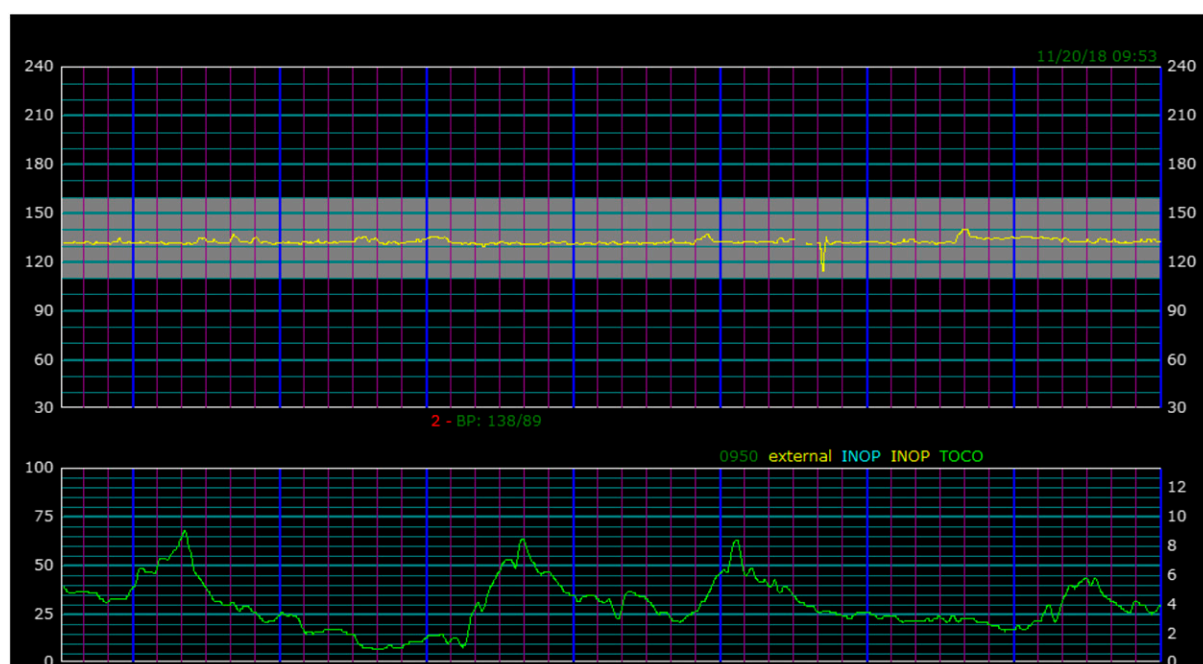


Figure 2. Electronic fetal monitoring strip 2.

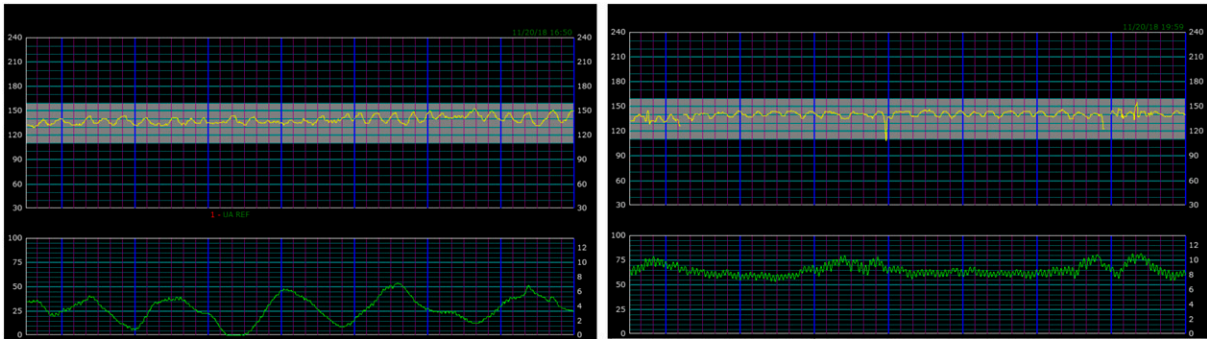


Figure 3. Electronic fetal monitoring strip 3.

or beyond. Recognizing the higher-risk postterm population is often rather challenging. The spontaneous onset of labor and the trigger that begins this physiologic process between the pregnant woman and fetus is not well understood. Pregnancies that progress beyond the 10 months allotted for human gestation are therefore subjected to labor induction, exposure to medications, and an extended time in L&D compared with women admitted in spontaneous active labor. In addition, women undergoing labor induction are offered, and often require, more pain medication. Our case demonstrates a late-term induction of a low-risk nulliparous woman who arrived in the L&D department with a category I FHR tracing.

The woman in this case received continuous epidural medication for more than 34 hours and developed a

pseudosinusoidal pattern. In a prospective observational study, this pattern was found to occur in 15% of laboring women. (1) The study demonstrated an independent association of pseudosinusoidal FHR patterns with meperidine and epidural analgesia, which often contains opioids such as morphine and fentanyl. The authors reported that these patterns are usually associated with normal outcomes, but careful fetal assessment is mandatory.

The fetal effects of opioids administered through the epidural space are rarely discussed in the current medical literature. Most providers believe that there is no narcotic exposure to the fetus if drugs are administered through the epidural space compared with the intravenous route. The epidural space is a space anterior to the dura mater, the third

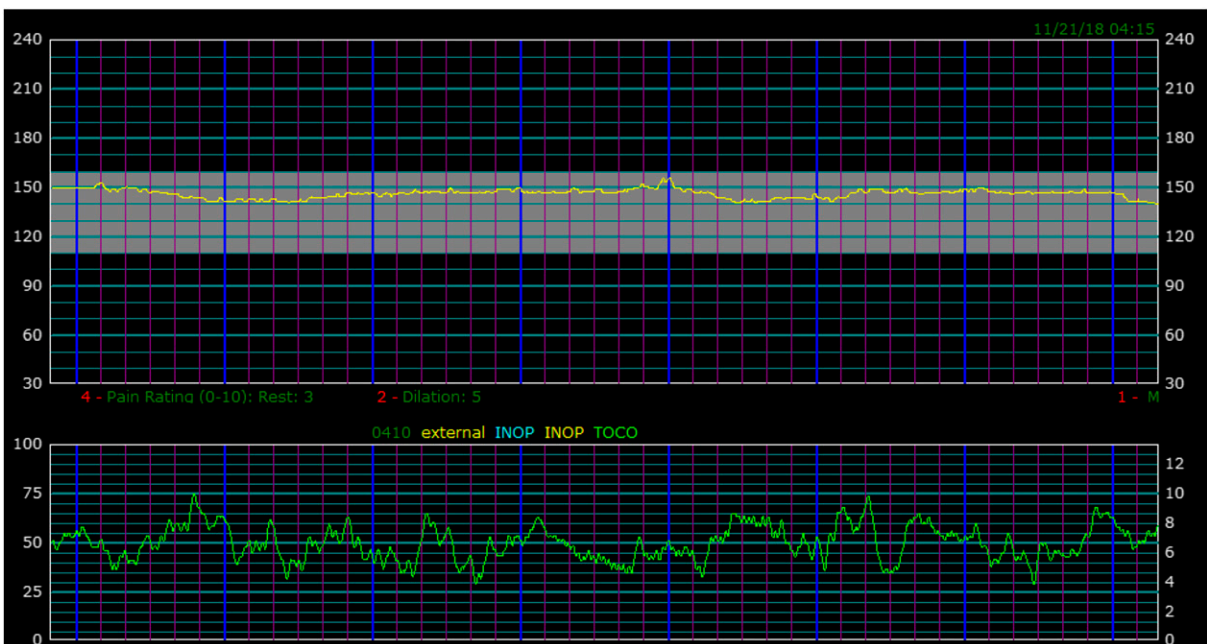


Figure 4. Electronic fetal monitoring strip 4.



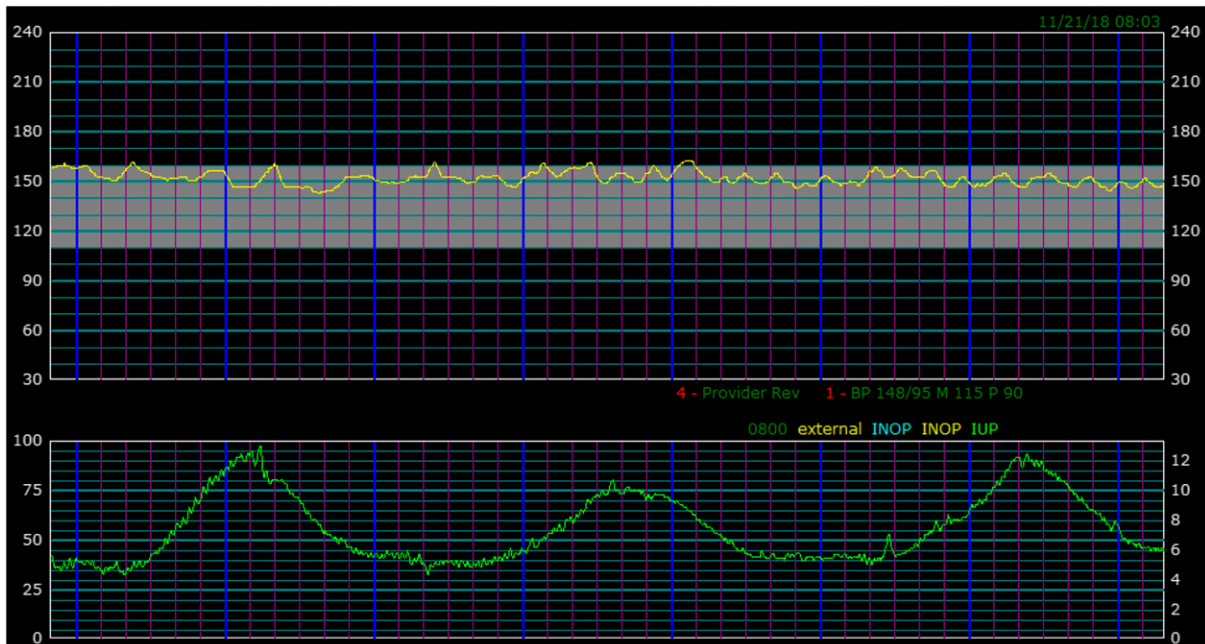


Figure 5. Electronic fetal monitoring strip 5.

layer of the meninges that covers the central nervous system (CNS), which has superior and inferior ligamentous boundaries, and contains small blood vessels and fat tissue that absorbs injected medications. Medication placed in the epidural space can diffuse into the CNS of the pregnant

woman, or can be absorbed into the general systemic circulation. (2) As such, fetal exposure to anesthetic medication placed in the epidural space can result in FHR changes either directly through the systemic circulation, through an increase or decrease in uterine tone, and less

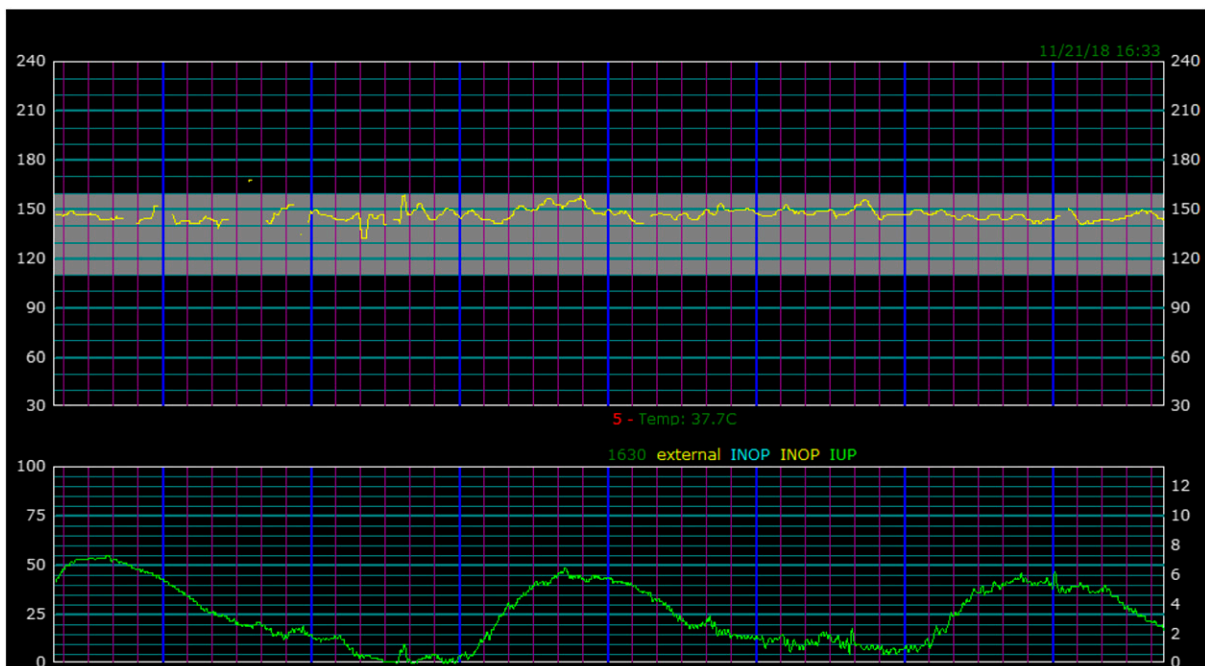


Figure 6. Electronic fetal monitoring strip 6.

TABLE 2. Arterial Gas Values of the Neonate

ARTERIAL GAS	NEONATE	REFERENCE RANGE
pH	7.11	7.35 to 7.45
Pco <sub>2</sub> (mm Hg)	67	35.0 to 45.0
PO <sub>2</sub> (mm Hg)	32	80 to 100
Base excess (mmol/L)	−8.00	−10.00 to −2.00
Hco <sub>3</sub> (mmol/L)	20	22.0 to 28.0

commonly, because of maternal hypotension. The fetus in this case was significantly depressed at the time of delivery and there were no other factors except for medication exposure to explain this outcome. Neonatal hypermagnesemia could also cause neonatal hypotonia but even though the woman was hypertensive, she was not treated with magnesium sulfate. Despite the initial perinatal depression, the infant responded to resuscitative efforts.

The National Institute of Child Health and Human Development standard FHR terminology defines the sinusoidal FHR pattern, but does not comment on pseudosinusoidal patterns. However, the recommendations urge clinicians to determine whether the FHR pattern is reassuring or non-reassuring because reassuring patterns are not associated with fetal acidemia and non-reassuring patterns may suggest worsening fetal status, or the need for alternative assessment to reassure the provider of fetal well-being. (3) Deliveries in which the FHR tracing demonstrates a pseudosinusoidal pattern should, at the very least, include the pediatric team who are prepared to resuscitate and if need be, intubate the infant, because the neonatal status is unpredictable with pseudosinusoidal patterns.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how to assess fetal well-being during labor.
- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor including reassuring and nonreassuring and indeterminate patterns.
- Know the effects on the fetus and/or newborn infant of analgesics and anesthetics administered to the mother during labor.

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## Strip of the Month: Pseudosinusoidal Pattern in Labor

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**Strip of the Month: Pseudosinusoidal Pattern in Labor**

Kafui A. Demasio

*NeoReviews* 2019;20:e475

DOI: 10.1542/neo.20-8-e475

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## A Newborn with “Black Spots”

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### THE CASE

A newborn presents with “black spots” all over the body.

#### Prenatal and Birth Histories

- Born to a 20-year-old gravida 2 para 1 black woman with a history of 1 spontaneous miscarriage
- Prenatal course unremarkable; normal prenatal fetal survey
- Estimated gestational age: 38 6/7 weeks
- Cesarean section due to failure of progression of labor
- Prenatal maternal laboratory findings: HIV negative, hepatitis surface antigen negative, nontreponemal screening negative, and rubella immune; group B *Streptococcus* screening positive at 38 weeks' gestation
- Intrapartum fever with temperature recorded at 101.3°F (38.5°C); vancomycin administered 6 hours before delivery because of a documented maternal allergy to penicillin
- Apgar scores: 9 and 9 at 1 and 5 minutes, respectively

#### Presentation

The infant was admitted to the NICU for evaluation of possible infection because of suspected maternal chorioamnionitis. On physical examination, the infant was active. The infant had more than 20 brown and black macules and patches on the trunk and the lower extremities (Figs 1 and 2). An 11-cm sharply circumscribed brownish black plaque with verrucous texture and no visible hair follicles was noted and involved the entire left side of the scalp, sparing the occipital region (Fig 3).

The mother's medical history was significant for 20 nonmalignant black macules and patches on her back, mainly in the interscapular region. The infant's maternal grandmother reported similar skin lesions over her body, with dense distribution on the lower extremities.

### PROGRESSION

#### Vital Signs

- Heart rate: 146 beats/min
- Respiratory rate: 42 breaths/min
- Blood pressure: 68/32 mm Hg (mean 47 mm Hg)
- Oxygen saturation: 97% (in room air)
- Temperature: 99°F (37.2°C)

#### Physical Examination (Day 1)

- Birthweight 3,402 g (54th percentile), length 49.5 cm (43rd percentile)
- Head: Normocephalic; normal, open, flat fontanelles; symmetric facies; patent nares; intact palate; no neck mass or crepitus

**AUTHOR DISCLOSURE** Drs Shi and Kurada have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Multiple hyperpigmented lesions on the back.

- Oral cavity: Pink mucosae, intact palate, no lymphadenopathy, normal sucking and rooting reflex
- Lungs: Clear, equal breath sounds; no respiratory distress
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallops
- Abdomen: Soft, nontender, no masses; umbilical stump clean and dry
- Genitourinary: Normal term male genitalia; patent anus
- Skeletal: Spine appears normal
- Skin: Multiple brown and black macules and patches on scalp, trunk, and the lower extremities
- Neurologic: Easily aroused, symmetric Moro reflex, normal strength and tone

#### Laboratory Studies

- White blood cell count:  $14,900/\mu\text{L}$  ( $14.9 \times 10^9/\text{L}$ ) with 52% neutrophils, 30% lymphocytes
- Red blood cell count:  $5.11 \times 10^6/\mu\text{L}$  ( $5.11 \times 10^{12}/\text{L}$ )
- Hemoglobin: 17.5 g/dL (175.0 g/L)



Figure 2. Multiple hyperpigmented lesions on the lateral of thigh.

- Platelet count:  $352 \times 10^3/\mu\text{L}$  ( $352 \times 10^9/\text{L}$ )
- C-reactive protein: Negative
- Blood culture: Sent

#### DIFFERENTIAL DIAGNOSIS

- Blueberry muffin rash
- Familial lentiginosis syndrome
- LEOPARD syndrome
- Congenital melanocytic nevi
- Congenital blue nevi
- Congenital dermal melanocytic lesion

#### ACTUAL DIAGNOSIS

##### Congenital Melanocytic Nevi

The infant received a 5-day course of empiric antibiotics for possible infection in the NICU. Oral feedings were initiated on the day of admission and advanced as tolerated. Complete blood cell count did not show an elevation of immature white blood cells and the C-reactive protein was normal 24 and 48 hours after delivery. The infant's blood culture specimen obtained before initiation of antibiotics was sterile and placental histopathology did not show evidence of chorioamnionitis. Antibiotics were discontinued after 5 days.

Findings of other investigations, including a complete retinal examination and brain ultrasonography, were unremarkable. At discharge, the infant received a follow-up evaluation by pediatric neurology and dermatology to monitor the progress of the nevi. Magnetic resonance imaging (MRI) of the infant's brain and spine was planned as an outpatient procedure.

#### WHAT THE EXPERTS SAY

Melanocytic nevi are benign proliferations of "nevus cells." (1) They are classified as either acquired or congenital. Congenital melanocytic nevi (CMN) occur in approximately 1% of neonates, and can present either at birth or develop within the first few postnatal months. (2) The size of the CMN is important because large or giant CMN are more likely to be associated with various tumors such as melanoma and neurocutaneous melanocytosis (NCM). The definition of giant CMN in an infant is 9.0 cm on the head or 6.0 cm on the body. (3) The prevalence of giant CMN is approximately 1 in 20,000 births. (4) On the contrary, acquired melanocytic nevi usually occur after infancy and commonly grow in both size and number until the fourth decade of age. (3)

The risk of developing melanoma in patients with large or giant CMN is up to 5%. Half of them occur before age 5





Figure 3. A large brownish black plaque on the scalp.

years. (5) The factors associated with increased risk of melanomas in neonates with CMN are: 1) large CMN with a projected adult size between 40 and 60 cm in diameter; 2) a truncal location, especially involving the spine; 3) numerous (eg, >20) satellite nevi. (6)

In contrast, melanoma is less likely to develop if the CMN are limited to the head and neck or an extremity only. (7) The risk factors of CMN and NCM are similar: a large CMN and numerous satellite nevi (eg, >20) have been reported to be associated with NCM. (8)

Early MRI screening (before 4 months) of the brain and spine of asymptomatic neonates with “high-risk” CMN is recommended because up to 25% of patients present with abnormalities on an MRI despite seemingly normal findings on neurologic examination. A normal MRI may be reassuring because these infants are less likely to develop symptomatic NCM. (9) If imaging is performed after age 4 months, it may be difficult to detect subtle melanotic foci with myelination of the central nervous system.

Surgical excision of large CMNs is recommended as prophylaxis against the development of melanoma. In some cases, surgery becomes challenging because of the extensive depth and size of the nevi. Common complications of surgery include need for anesthesia, discomfort, or post-operative restriction of function. Recurrence of nevi and the development of melanoma after excision warrant long-term postsurgical follow-up. (10)

The differential diagnosis of multiple hyperpigmented lesions in neonates includes the following:

1. Blueberry muffin rash: In contrast to black/brown hyperpigmentation, blueberry muffin rash commonly presents with 2- to 10-mm, nonblanching, magenta-to-violaceous papules and macules. Common causes that

lead to this rash, such as toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections, blood incompatibility, and malignancies (eg, congenital leukemia), were not supported by unremarkable laboratory findings.

2. Familial lentiginosis syndromes: These are characterized by multiple small, well-circumscribed brown macules (often <5 mm) as lentigines have increased numbers of melanocytes. The size of skin lesions in our case varied, with some more than 1 cm.
3. LEOPARD syndrome can present with brown macules. It refers to a syndrome with systemic manifestations (lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth restriction, and deafness (sensorineural). The current infant had no dysmorphic features, normal vital signs as well as growth parameters, and passed the hearing test.
4. Congenital blue nevi: Skin lesions include a rash that is bluish rather than brown/black. Blue nevi produce melanin and present with blue-gray to blue-black nodules or plaques with a smooth or mammillated surface. Cellular blue nevi are usually 3 cm or smaller in diameter, but large lesions can occur.
5. Congenital dermal melanocytic lesion: Mongolian spots and nevus of Ota/nevus of Ito are major congenital dermal melanocytic lesions commonly seen in neonates. Mongolian spots are usually in lumbosacral areas with variant ranges from a small macule to a huge patch.

Given the unremarkable prenatal maternal laboratory results, an active and healthy-appearing infant, as well as color, size, and pattern of the skin lesions, CMN is the most likely diagnosis in this infant.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the differential diagnosis and syndromes associated with hyperpigmented lesions, including cafe au lait spots, Peutz-Jeghers syndrome, giant hairy nevus, incontinentia pigmenti, and pigmented nevi.
- Know the etiology and cutaneous manifestations of common neonatal skin lesions, including erythema toxicum, neonatal pustular melanosis, and neonatal acne.
- Know the management of common neonatal dermatoses, including diaper dermatitis.

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## Emergent Neonatal Abdominal Paracentesis: A Step-by-Step Video Simulation

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### 1. INDICATIONS

- a. Evacuation of ascites with resultant cardiorespiratory compromise.
- b. Signs of ascites with resultant cardiorespiratory compromise.
  - i. Signs:
    1. Tense abdominal distention.
    2. Hypoxia or bradycardia despite adequate ventilatory efforts and no other clear etiology, particularly in the setting of prenatally diagnosed or postnatally apparent abdominal ascites or hydrops fetalis.
  - ii. The aforementioned signs may not always be present.

### 2. CONTRAINDICATIONS

- a. There are no absolute contraindications to this procedure in an emergent setting.
- b. This is an invasive procedure and should not be performed if the decision has been made for redirection unless approved by the family.
- c. Relative contraindications:
  - i. Massive hepatosplenomegaly:
    1. If isolated hepatomegaly is present, consider using the left lower quadrant for needle insertion.
    2. If isolated splenomegaly is present, consider using the right lower quadrant for needle insertion.
  - ii. Large abdominal wall defects overlying site of needle insertion.
  - iii. Bleeding disorder including severe thrombocytopenia or coagulopathy.
- d. All relative contraindications, risks, and benefits need to be assessed in the context of an emergent situation.
  - i. If the procedure is being performed in a high-risk situation, strongly consider ultrasound guidance if it is available in your institution.



**AUTHOR DISCLOSURE** Drs Matrone, Cacho, Weiss, and Ruoss have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Video.** A step-by-step video about how to perform a paracentesis in a neonate.

### 3. CONSENT

- a. This video provides instruction on how to perform an abdominal paracentesis in an emergency (Video). Consent is not routinely obtained before performing this procedure in an emergent setting.
- b. It is appropriate to discuss the procedure with the parent(s)/guardian(s) if time permits and parent(s)/guardian(s) are readily available during the resuscitation.
- c. If there is not an opportunity to discuss with the parent(s)/guardian(s) before the procedure, it should be discussed with them as soon as possible after the procedure is performed.

### 4. TIME OUT

- a. Before performing the procedure, discuss the reason for the procedure and the patient's name.
- b. A time out should be performed even in an emergency.

### 5. EQUIPMENT

- a. 2% chlorhexidine gluconate, alcohol swabs, or the recommended antiseptic solution at your institution
- b. 18- or 20-gauge angiocatheter
- c. 5-mL syringes
- d. 2-mL syringes
- e. 3-way stopcock
- f. Sterile gloves, hat, and mask; if time permits, sterile gown
- g. Materials for sterile dressing including sterile gauze and adhesive
- h. Optional: Sterile container to send cultures and diagnostic studies

### 6. ANATOMY

- a. The needle is inserted in the left or right lower abdominal quadrant, halfway between the umbilicus and anterior superior iliac spine.

### 7. PREPARATION

- a. Discuss the procedure with parent(s)/guardian(s) if possible. Otherwise, discuss with parent(s)/guardian(s) as soon as feasible once the infant is stabilized.
- b. Have all equipment listed available at bedside.
- c. Perform a preprocedure time out immediately before procedure. Confirm patient identification, procedure, indication, and site.
- d. Providers performing the procedure should perform routine hand hygiene and use sterile gloves.

- e. If possible, even in the emergency delivery room setting, place the patient on a heart rate and oxygen monitor while the procedure is being performed.

### 8. PERFORMING THE PROCEDURE

- a. Position patient in supine position
- b. Rapidly inspect abdominal wall
  - i. Note any congenital abnormalities or abdominal wall defects
- c. Rapidly palpate the abdomen
  - i. Palpate and note location of anterior superior iliac spines bilaterally
  - ii. Consider marking these landmarks for orientation during procedure
- d. Mark site with pen or indentation
  - i. Select one side of abdomen, consider left if no contraindication to avoid liver
  - ii. Identify the location halfway between umbilicus and anterior superior iliac spine in the lower abdominal quadrants
- e. Apply hat and mask. Use sterile gown if appropriate for the setting in which you are performing the procedure
- f. Wash hands and apply sterile gloves
- g. Confirm that supplies are prepared
  - i. Using aseptic precautions, attach 18- to 20-gauge angiocatheter to 5-mL syringe
  - ii. Have additional 20-mL sterile syringes with additional 3-way stopcock available if needed
- h. Prepare marked skin site and surrounding skin with 2% chlorhexidine gluconate or other appropriate product as available
  - i. Use circular motion of scrub, center to peripheral
  - ii. Allow enough time for preparation material to fully dry before needle insertion
- i. Needle insertion: "Z-tracking" versus insertion perpendicular to skin in marked area
  - i. Z-tracking:
    1. Gently pull up on superficial skin
    2. Point needle caudal then cephalad as you advance the needle
  - ii. Perpendicular insertion:
    1. Insert needle perpendicular to skin and advance posteriorly (attached video uses this technique)
- j. Provide continuous aspiration while slowly inserting 18- to 20-gauge angiocatheter with needle
- k. Stop insertion of needle when fluid returns in attached 5-mL syringe
- l. Slide catheter over the needle and then withdraw needle



- m. Appropriately dispose of needle
- n. Attach a 20-mL syringe with or without a 3-way stopcock to angiocatheter
- o. Slowly aspirate ascitic fluid in 15- to 20-mL aliquots
  - i. Continue fluid removal as necessary for resolution of cardiorespiratory compromise or until no additional fluid can be drawn back
- p. Consider transferring fluid to sterile container or capping sterile syringe
  - i. Fluid may be sent for diagnostic studies and culture
- q. Pull out the angiocatheter, gently apply pressure to site, and then apply sterile bandage
- r. Dispose of needle in sharps container, if not already done
- s. Reassess patient for procedural complications including hematoma, signs of intraperitoneal hemorrhage, continued leak from insertion site, or signs/symptoms of bowel or bladder perforation
- t. After stabilization, document procedure and time out in patient medical record

## 9. POTENTIAL COMPLICATIONS

- a. Perforation of the intestine with or without pneumoperitoneum
- b. Perforation of the bladder
- c. Perforation of the liver or spleen with or without intraperitoneal hemorrhage
- d. Persistent fluid leak
- e. Infection
- f. Hematoma at needle insertion site

## 10. ADDITIONAL INFORMATION

- a. Ideally, ultrasonography should be performed before and during this procedure to minimize complications. However, in an emergent setting when ultrasonography

cannot be performed in a timely manner, it is important for the practitioner to know how to perform the steps of this life saving procedure.

The checklist was validated using the Delphi process and was reviewed by 10 expert specialists including neonatologists, pediatric intensivists, and pediatric surgeons.

## American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the diagnostic evaluation and perinatal management of fetal-maternal blood group incompatibility.
- Know the differential diagnosis and the plan of evaluation and management of a fetus with non-immune hydrops.
- Know the etiology, clinical manifestations, diagnostic features, and management of neonatal ascites.

## Suggested Readings

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# Noninvasive Ventilation in the Delivery Room for the Preterm Infant

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## Education Gaps

The preterm lung is highly susceptible to injury from exposure to mechanical ventilation in the delivery room. It is important to use optimal noninvasive ventilation strategies and continuous positive airway pressure to establish functional residual capacity during resuscitation to avoid intubation and mechanical ventilation.

## Abstract

A decade ago, preterm infants were prophylactically intubated and mechanically ventilated starting in the delivery room; however, now the shift is toward maintaining even the smallest of neonates on noninvasive respiratory support. The resuscitation of very low gestational age neonates continues to push the boundaries of neonatal care, as the events that transpire during the golden minutes right after birth prove ever more important for determining long-term neurodevelopmental outcomes. Continuous positive airway pressure (CPAP) remains the most important mode of noninvasive respiratory support for the preterm infant to establish and maintain functional residual capacity and decrease ventilation/perfusion mismatch. However, the majority of extremely low gestational age infants require face mask positive pressure ventilation during initial stabilization before receiving CPAP. Effectiveness of face mask positive pressure ventilation depends on the ability to detect and overcome mask leak and airway obstruction. In this review, the current evidence on devices and techniques of noninvasive ventilation in the delivery room are discussed.

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### ABBREVIATIONS

BPD	bronchopulmonary dysplasia
CPAP	continuous positive airway pressure
DR	delivery room
EtCO <sub>2</sub>	end-tidal carbon dioxide
FRC	functional residual capacity
GA	gestational age
HFNC	high-flow nasal cannula
IVH	intraventricular hemorrhage
NRP	neonatal resuscitation program
PEEP	positive end-expiratory pressure
PIP	peak inspiratory pressure
PPV	positive pressure ventilation
RCT	randomized controlled trial
SI	lung inflation
V <sub>T</sub>	tidal volume

## Objectives After completing this article, readers should be able to:

1. Describe the fetal to neonatal transition in the lung.
2. Explain the importance of establishing functional residual capacity for successful noninvasive respiratory support.
3. Describe the modes of noninvasive respiratory support and list the devices used for premature infants at time of birth.

## FETAL TO NEONATAL TRANSITION

The critical period of fetal lung development occurs during the canalicular to saccular stages. Premature infants are born in this critical period and therefore are at highest risk for lung underdevelopment and injury. For the lung to develop properly, the lung must be fluid-filled. In utero, the fetal lung epithelium secretes liquid, allowing for the lungs to be fluid-filled. (1)(2) With the help of a closed fetal larynx that prevents fluid from flowing out of the lung, the fluid creates lung expansion that is important for the normal development of the lung. During this time, fetal gas exchange relies solely on the placenta. (1)(2) The low oxygen tension in the alveoli results in a state of constant pulmonary vasoconstriction in the fetus, which diverts blood from the lungs to the systemic circulation.

As gestation advances, multiple changes prepare the fetal lung for an ex utero environment, including the differentiation of type I and II pneumocytes, the secretion of surfactant to reduce alveolar surface tension, and the modification of epithelial sodium channels. Signals around the time of birth lead to an increase in catecholamine release that downregulates fluid secretion by the lung epithelium and stimulates fluid resorption by the sodium channels, changing the lungs from fluid-filled to gas-filled. (1) Once the lung is gas-filled, the oxygen tension increases and leads to nitric oxide-mediated pulmonary vasodilation and gas exchange. At birth, all of these pulmonary changes help to facilitate the neonatal lung in establishing functional residual capacity (FRC). However, several factors impede the development of adequate FRC among preterm infants, including immature lung parenchyma, surfactant deficiency, a compliant chest wall, slower lung fluid clearance, weak respiratory muscle, poor laryngeal tone leading to decreased ability to grunt, and an immature respiratory drive. (3)(4)(5) Preterm infants often require positive pressure ventilation (PPV) soon after birth because of poor FRC and ineffective respiration that may be associated with bradycardia.

While the majority of preterm infants (65%–77%) born at less than 28 weeks' gestational age (GA) require PPV in the delivery room (DR), (6)(7) they are also the most vulnerable to the adverse consequences that may arise from exposure to PPV. Even brief exposure to large tidal volume ( $V_T$ ) breaths can initiate an inflammatory cascade that alters lung architecture and contributes to the development of bronchopulmonary dysplasia (BPD). (8)(9)(10) Meta-analyses of large, multicenter, randomized controlled trials (RCTs) that evaluated invasive and noninvasive respiratory support in the DR show that avoiding intubation and stabilizing infants on

continuous positive airway pressure (CPAP) decreases the composite outcome of death or BPD. (11)(12) DR management for the premature infant may have an extremely important effect on survival and survival without severe illness. (13)(14) These findings have resulted in a practice change, with an increasing number of infants in the DR being stabilized on CPAP. (15)(16)(17) The aim of this article is to provide an updated review of noninvasive devices and strategies used in the DR for premature infants (Table 1).

## INTERFACES FOR DELIVERING NONINVASIVE PPV IN THE DR

### Face Mask

Administration of noninvasive PPV via face mask is the current standard of care. Two different types of masks are available for use: an anatomic shaped mask and a round mask. Face mask PPV is dependent on achieving an adequate seal to avoid mask leak. Commercially available masks vary in shape and size (Fig 1). Palme et al compared 5 widely used round and triangular masks for mask leak in 44 newborns in the DR. (18) They assessed the percentage of leak by calculating the difference between set pressure and the average peak pressure. This study reported less leak with the use of the round silicone mask compared with the triangular mask. (18) However, O'Donnell et al compared round and anatomic masks using mannequins and found no difference in the air leak between the 2 different mask types. (19)

O'Shea et al evaluated the facial measurements of preterm infants born between 24 and 33 weeks' GA and suggested that masks of 35-mm diameter are suitable for infants of less than 29 weeks' GA and 42-mm diameter masks are suitable for infants between 27 and 33 weeks' GA. Interestingly, the standard commercially available face mask measures 50 mm while small round face masks are available in 35-mm and 42-mm inner diameter sizes. (20) The correct mask size should be determined by placing the bottom of the mask on the tip of the chin to cover the mouth and the nose but the top of the mask not reaching the eyes. However, a recent RCT that measured the mask leak using respiratory function monitoring did not show any difference in the mask leak between standard and small round masks. (21)

There are several ways to hold the face mask (Fig 2). A recent study looking at corrective ventilation strategies for infants of less than 32 weeks' GA in the DR found that the most frequent mask holds were 1-handed (95%), 2-handed (63%), stem hold (23%), and modified spider hold (6%). (22) The mask hold also depends on the face mask that is being

**TABLE 1. Delivery Room Interfaces and Devices for Resuscitation**

Interfaces for delivering positive pressure ventilation
• Face mask (anatomical shaped vs round)
• Single nasal tube
• Short binasal prongs
Pressure delivery devices for delivering positive pressure ventilation
• T-piece resuscitator
• Flow-inflating bag
• Self-inflating bag

used, because a different hold may be necessary for the silicone face mask versus the bubble face mask.

There is a theoretical concern that when the face mask is placed, it overlies the nasotrigeminal area and can influence ventilation by stimulating the trigeminal nerve, resulting in cessation of a normal breathing pattern, bradycardia, peripheral vasoconstriction, and closure of the larynx. (23) This further necessitates proper face mask positioning and size to limit stimulation of this nerve.

### Single Nasal Tube

To overcome the shortcomings of the face mask, other interfaces such as nasal tubes and short binasal prongs are being studied for the delivery of noninvasive ventilation. A nasal tube is a single tube that enters one nare and ends in the nasopharynx and is used to deliver PPV. Van Vonderen et al, in their study of 43 infants, used nasal tubes as the primary mode to deliver noninvasive ventilation and found

more leak and tube obstruction with the nasal tube compared with a face mask. (24) In addition, using the nasal tube delayed PPV initiation because of placement of the tube, and was also noted to be associated with inadequate  $V_T$ . (24)

### Short Binasal Prongs

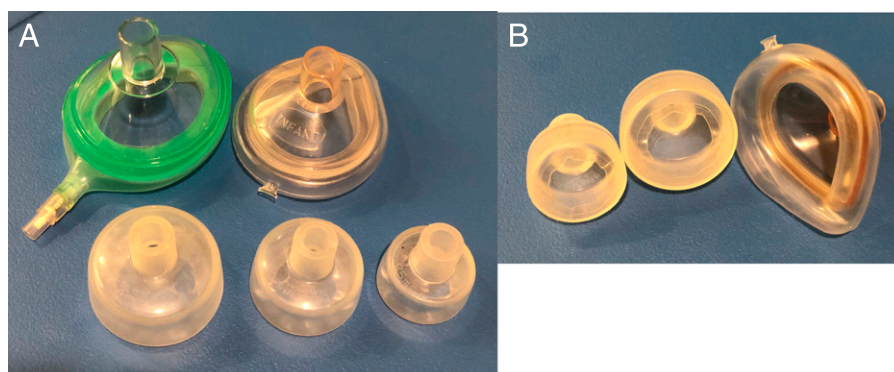
Although binasal prongs are widely used to provide CPAP in the DR, the experience with its application for providing PPV in the DR is limited. To date, the RAM Cannula (Neotech, Valencia, CA) is the only nasal prong that is able to directly interface with the T-piece resuscitator. A single-center retrospective study reported a decrease in DR intubation rate after instituting these particular short binasal prongs to provide noninvasive ventilation compared with historical cohorts who were resuscitated with a face mask. (25) However, theoretical concerns exist including possible higher intrinsic resistance (26) and insignificant  $V_T$  delivery with ventilator-delivered noninvasive positive pressure breaths. (27)

In summary, there is no current evidence to suggest one mask is better than another for neonatal DR resuscitation, although mask size is important. Other interface options such as a single nasal tube and short binasal prongs need to be evaluated further in well-designed RCTs before being adopted for routine clinical practice. Simulation-based training has been shown to decrease mask leak and improve the effectiveness of face mask PPV.

## MODES OF NONINVASIVE RESPIRATORY SUPPORT IN THE DR

### Positive Pressure Ventilation

The Neonatal Resuscitation Program (NRP) currently recommends initiating PPV in the DR for bradycardia ( $HR < 100$ ) and/or when respiratory effort by the neonate is inadequate. (28) The recommended initial settings are an



**Figure 1.** Examples of face masks. A. The top row demonstrates anatomic face masks. The bottom row demonstrates round face masks. B. Anatomic masks (mask at far right) have an air-filled balloon whereas round masks (mask at far left and in the middle) have a silicone flap to promote adherence to the face without excessive downward pressure.

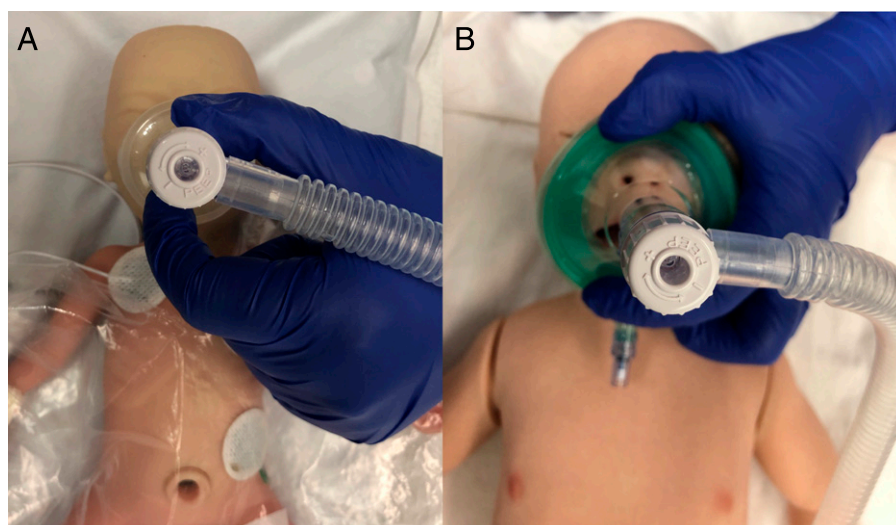


Figure 2. Examples of mask holds. A. Stem hold. B. One-handed ("C") hold.

inflation pressure of 20 cm H<sub>2</sub>O, and positive end-expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O at a rate of 40 to 60 breaths/min, with the pressure being adjusted depending on the patient's response. Response to PPV can be evaluated by improvement in heart rate which can be monitored using electrocardiographic waveforms or pulse oximetry.

There are 3 modes to deliver PPV: a T-piece resuscitator, a self-inflating bag, or a flow-inflating bag (Fig 3), which are all approved by NRP to be used for resuscitation in the DR, depending on resources available at the hospital. It should be noted that only the flow-inflating bag and T-piece resuscitator can be used to provide PPV and CPAP. Use of a T-piece is gaining favor for DR use because of its ability to deliver controlled pressures. However, 3 RCTs comparing the use of a T-piece resuscitator versus a self-inflating bag for ventilation of extremely preterm infants in the DR did not show improvement in long-term outcomes. (29)(30)(31) A single-center observational study comparing the self-inflating bag to the T-piece resuscitator in very-low-birthweight neonates showed that the latter modality had an increased hospital survival rate without BPD, intraventricular hemorrhage (IVH), and periventricular leukomalacia. (32)




It is difficult for practitioners to estimate the V<sub>T</sub> being delivered during PPV despite the use of advanced resuscitation devices such as the T-piece resuscitator. One study showed that of 218 neonates born at less than 29 weeks' GA resuscitated in the DR, with the T-piece resuscitator set at a peak inspiratory pressure (PIP) of 24 and PEEP of 6 cm H<sub>2</sub>O, 75% of patients received ventilation with V<sub>T</sub> greater than 6 mL/kg, which can injure the lungs and contribute to IVH. (33) Fifty-one percent of infants who received

ventilation with large V<sub>T</sub> were diagnosed with IVH compared with a 13% rate of IVH in the group with a V<sub>T</sub> less than 6 mL/kg. (33) Hinder et al investigated T-piece devices on mannequins and showed that despite a set PEEP and PIP, the pressure being delivered to the individual neonate varied, depending on the changes in lung compliance. (34) Hinder et al also found that T-piece devices delivered inadvertent PEEP above the set value, possibly because of a number of factors, including accidental rotation of the PEEP knob, finger distance over the PEEP valve, presence of an endotracheal tube, use of surfactant, high airway resistance, and low delivery gas flowrate. (34) Further studies are needed to verify these findings.

### Sustained Lung Inflation

Sustained lung inflation (SI) is the use of distending pressure PIP applied for a certain duration with the goal of establishing FRC. In animal models, SI performed during the first inflations after birth helped to clear liquid from the airways and helped in establishing FRC. To date, 5 RCTs have investigated the use of SI in preterm infants using different durations and SI pressures. A meta-analysis comparing all patients from these trials showed no significant difference in the rate of BPD or death. (35) Recently, the Sustained Inflation of Infant Lung (SAIL) trial randomized 426 extremely preterm infants with bradycardia with inadequate respiratory effort in 9 countries to either 2 sustained inflations to maximal peak pressure of 25 cm H<sub>2</sub>O for 15 seconds or standard bag and mask. (36) The trial was stopped early because of increased death in the first 48 hours after birth in the sustained inflation group. (36) Currently, there is not enough evidence to recommend



T- piece resuscitator	Flow-inflating bag	Self-inflating bag
		
Provides CPAP	Provides CPAP	Does NOT provide CPAP (unless using PEEP valve)
Requires gas source	Requires gas source	No gas source required, refills spontaneously
Consistent PIP, PEEP	Inconsistent PIP, PEEP	Inconsistent PIP, PEEP
FiO <sub>2</sub> up to 1.0	FiO <sub>2</sub> up to 1.0	FiO <sub>2</sub> 0.21, unless using oxygen reservoir
Unknown Tidal Volume	Unknown Tidal Volume	Unknown Tidal Volume

**Figure 3.** Comparison of devices used to deliver positive pressure ventilation. CPAP=continuous positive airway pressure; PEEP=positive end-expiratory pressure; PIP=peak inspiratory pressure.

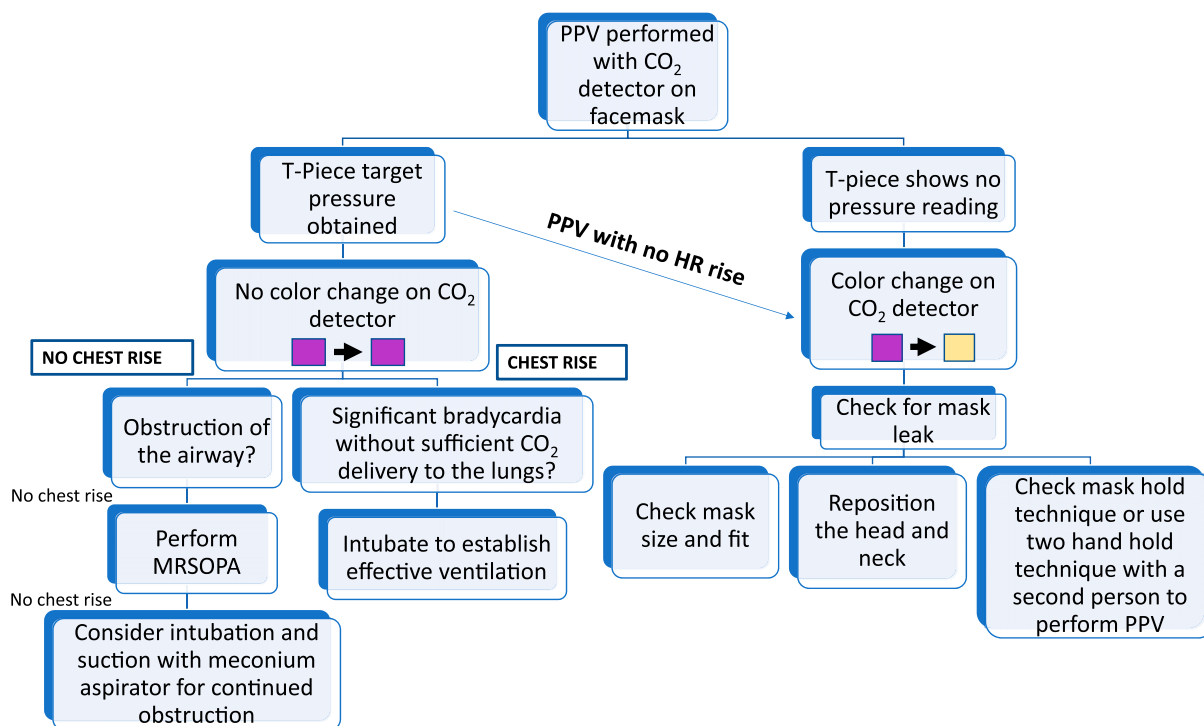
routine SI in the DR, and one RCT suggests potential harm with this approach.

#### Intervention to Overcome Mask Leak and Airway Obstruction

The best evidence that a neonate is receiving effective ventilation after initiation of PPV is a rising heart rate. Most premature infants will receive PPV in the DR. (6) When the heart rate fails to increase, the first step in troubleshooting is to address mechanical issues such as airway obstruction and mask leak. Premature infants are placed in plastic bags for thermoregulation and it is often difficult to assess chest rise through the bag. (37) To diagnose the potential issue leading to ineffective PPV, some studies suggest that the use of colorimetric end-tidal carbon dioxide (EtCO<sub>2</sub>) detection during face mask ventilation may be beneficial. Using a disposable EtCO<sub>2</sub> detector attached to a face mask during PPV, providers can assess the patency of the airway. (38)(39)(40)(41) In one observational study using EtCO<sub>2</sub> detectors, 18 infants received a median of 14 obstructed breaths defined by no color change on the EtCO<sub>2</sub> despite reaching a target pressure. (38) The authors concluded that airway obstruction is extremely common in very-low-birthweight infants and that EtCO<sub>2</sub> detectors can help recognize this obstruction. (38) In addition, in the neonate undergoing PPV with good chest rise, but continued bradycardia leading to poor cardiac output and insufficient carbon dioxide delivery to the lungs, EtCO<sub>2</sub> detectors may not change. This was found in a piglet model in which low quantitative EtCO<sub>2</sub> values were directly related to low cardiac output states, leading to decreased pulmonary blood flow. (42) Figure 4 describes

an algorithm for the practical use of EtCO<sub>2</sub> detectors in the DR. Importantly, when a target pressure cannot be obtained despite colorimetry change, this most likely represents mask leak. Of note, when using a T-piece device with a face mask, significant leak can occur while still visualizing the pressure reading on the manometer. Therefore, visualization of manometry pressures cannot be used to ensure reliable mask seal; practitioners must consider mask leak as a possible cause of ineffective PPV whether or not target pressure readings are obtained on the T-piece resuscitator.

After recognition of ineffective ventilation, NRP advises the use of the “MRSOPA” mnemonic to further correct ventilatory steps in a neonate with a decreasing heart rate. (28) Mask adjustment, repositioning the airway, suctioning, opening the mouth, increasing inspiratory pressure, and alternate airway (MRSOPA) are the most important steps in correcting ventilation. One observational study on the frequency and use of MRSOPA strategies in the DR found that infants less than 32 weeks’ gestation who received more MRSOPA interventions were more likely to be intubated. (22) However, a quality improvement project reported decreased DR intubation rates and improved outcomes with simulation-based peer-to-peer training on MRSOPA strategies by using small round masks, EtCO<sub>2</sub> detectors, increasing pressure, and increasing inspiratory time to 1 second when indicated. (17) Wood et al reported that team training using written instruction and photographs of the optimal techniques can help decrease mask leak during PPV. (43) Such interventions to improve ventilation via corrective steps conducted in individual centers can help decrease the need for intubation and increase stabilization of infants receiving noninvasive respiratory support in the DR.



**Figure 4.** Using end-tidal carbon dioxide (CO<sub>2</sub>) detectors attached to a face mask in the delivery room can help detect an obstructed airway. HR=heart rate; PPV=positive pressure ventilation; MRSOPA=mask adjustment, repositioning the airway, suctioning, opening the mouth, increasing inspiratory pressure, and alternate airway.

### CPAP for DR Resuscitation

CPAP has been widely used for the respiratory support of preterm infants in the NICU over the last 5 decades. (28)(44) CPAP increases FRC, (44) decreases airway resistance, (45) decreases thoracoabdominal asynchrony, (46) and decreases intrapulmonary shunting, (44) thus leading to better oxygenation and ventilation in spontaneously breathing preterm infants. In addition, CPAP helps decrease obstructive apnea (47) and augments surfactant production. (48) The devices and interfaces of CPAP use in the DR are listed in Table 2.

**Constant-Flow CPAP Devices.** T-piece resuscitator use with a face mask is recommended by NRP for CPAP delivery in the DR. (49) The desired PEEP level can be adjusted at the PEEP valve. The T-piece is used with a face mask, single nasal tube, or specific type of short binasal prongs (RAM cannula). Bubble CPAP uses the water column at the end of the expiratory limb to generate pressure in the CPAP circuit. CPAP level is determined by the immersion length of the expiratory tubing. (50) The gas exiting from the underwater tubing creates bubbles. Bubbling may provide additional benefits with mechanisms such as stochastic resonance (51) and high-frequency oscillatory waveforms (52) in improving gas exchange and lung recruitment. CPAP can also be delivered in the DR using an adjustable PEEP valve connected to the expiratory limb of the CPAP circuit. The inspiratory limb is connected to the gas source from the blender, usually set at a flow

rate of 8 to 10 L/min. Both bubble CPAP and the adjustable PEEP valve can be used with binasal prongs of many different types or small nasal masks. Ventilators are commonly used for CPAP delivery during transport and in the NICU rather than in the DR.

**Interfaces.** Although the face mask was routinely used to administer CPAP to infants with respiratory distress syndrome in the 1970s, it fell out of favor because of the difficulty in maintaining a proper seal. (53) However, CPAP is commonly administered with the T-piece resuscitator with the face mask in the DR because of the ability to provide PPV when indicated. As discussed before, maintaining a proper seal is important to provide the desired CPAP level. In addition, the increased dead space of the face mask also may decrease the effectiveness of CPAP delivery. (54)

Binasal prong CPAP has been effectively used since 1973. (50)(55) De Paoli et al demonstrated that short binasal prongs offered the lowest resistance to flow compared with the single nasal tube. (56) Prong size is an important consideration because the smaller prongs may generate higher resistance to flow. (56)(57) Small nasal masks can be used as an alternative to binasal prongs. Recently, Green et al reported that these small nasal masks pose less intrinsic resistance compared with short binasal prongs. (26)

**CPAP Delivery in the DR.** Face mask CPAP provided at 5 cm H<sub>2</sub>O using a T-piece generator should be initiated at



**TABLE 2. CPAP Devices and Interfaces for DR Resuscitation**

Constant flow CPAP generators
• T-piece resuscitator
• Bubble CPAP
• Adjustable PEEP valve
• Ventilator
Interfaces
• Face mask
• Single nasal tube
• Binasal prongs
• Small nasal masks

CPAP=continuous positive airway pressure; PEEP=positive end-expiratory pressure.

birth for all spontaneously breathing infants. Face PPV should be provided when the infant has bradycardia, poor respiratory effort, or both. CPAP should be restarted when the infant shows spontaneous respiratory effort and a stable heart rate. Manometer reading and EtCO<sub>2</sub> detectors can help in identifying mask leak while administering CPAP. Fraction of inspired oxygen is titrated using the NRP algorithm. (49) Although the titration of CPAP level in DR resuscitation has not been evaluated in clinical trials, one large RCT that routinely used 8 cm H<sub>2</sub>O reported a higher rate of pneumothoraces. (58) Subsequent trials that used CPAP levels of 5 to 7 cm H<sub>2</sub>O did not report higher rates of pneumothorax. (6) Higher CPAP levels can help achieve higher FRC. (44)(59) Therefore, CPAP level may be titrated higher—up to 7 cm H<sub>2</sub>O for infants requiring higher supplemental oxygen in the DR. When the infant demonstrates regular respiration, stable heart rate, and stable oxygen saturation, the infant can be transitioned to either binasal prong or small nasal mask for transport to the NICU. CPAP can be provided during transport in multiple ways, including bubble CPAP, an adjustable PEEP valve using gas flow, or ventilator CPAP. When using binasal prongs, it is important to use the binasal prong with the largest inner diameter that can snugly fill the nares.

### High-Flow Nasal Cannula

High-flow nasal cannula (HFNC) delivers heated and humidified gas that aids in gas exchange by minimizing dead space. (60) The pressure that is generated by HFNC is

determined by the flow rate, size of the nasal cannula, and amount of leak from the nose and mouth. (61)(62) Only 1 study has demonstrated the feasibility of using HFNC in the DR for infants between 23 and 29 weeks' GA. (63) HFNC in the DR is not recommended before well-designed RCTs.

### SUMMARY

During the delivery of premature infants, the DR can often be chaotic, given that premature deliveries could happen unexpectedly. A skilled resuscitation team is necessary to provide initial lifesaving breaths to this vulnerable population to quickly and effectively establish FRC. After establishment of FRC, maintaining neonates on CPAP to prevent lung injury with mechanical ventilation is well-studied. However, providing noninvasive ventilation can have challenges including mask leak, incorrect mask size, and airway obstruction. Use of a properly sized mask with a colorimetric EtCO<sub>2</sub> detector provides early feedback for airway obstruction and mask leak, though RCTs are still needed. Performing MRSOPA in the event of ineffective ventilation is the most important step to ensure the successful transition from PPV to CPAP in the DR.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the indications for assisted ventilation, including continuous positive airway pressure, immediately after birth and how to assess its effectiveness.
- Understand how to use self-inflating and flow-inflating bags or T-piece resuscitators to provide assisted ventilation immediately after birth.
- Know the mechanism of production and factors affecting the clearance of fetal lung liquid, its contribution to amniotic fluid, and its importance to fetal lung development.
- Know the effects of surface tension on alveolar and airway stability and lung mechanics (LaPlace law).
- Know factors that determine residual lung volume, functional residual capacity, and tidal volume, and how they change with various pulmonary disorders.
- Know the clinical features of an infant with airway obstruction.
- Know the indications for and techniques of continuous positive airway pressure (CPAP).
- Know the effects and risks of CPAP.

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1. The team is preparing for the delivery of an infant at 25 weeks' gestational age. Which of the following statements regarding anticipation of respiratory management for this infant is correct?
  - A. With optimal care including antenatal steroids and cesarean delivery, less than 20% of infants at this gestational age will require positive pressure ventilation in the delivery room.
  - B. Brief exposure to large tidal volume breaths, even immediately after birth, can initiate an inflammatory cascade that alters lung architecture and contributes to the development of bronchopulmonary dysplasia.
  - C. Even if it is not absolutely needed, the delivery of 10 to 20 carefully adjusted positive pressure ventilation breaths in a prophylactic fashion for all newborns in this circumstance will lead to decreased need for intubation and reduced incidence of respiratory distress syndrome and bronchopulmonary dysplasia.
  - D. Continuous positive airway pressure should be avoided until stabilization has progressed in the NICU to avoid pneumothorax.
  - E. The main factor that will drive respiratory management in the first few minutes, particularly in the decisions surrounding positive pressure ventilation, is oxygen saturation measurement.
2. A male infant born at 26 weeks' gestational age is handed to the pediatrics team after 60 seconds of delayed cord clamping. The infant has spontaneous respirations at first, but proceeds to have apnea and bradycardia. The patient is given positive pressure ventilation. Which of the following statements regarding the interface for delivering positive pressure ventilation is correct?
  - A. The first-line treatment for this patient should be endotracheal intubation.
  - B. Nasal prongs have proven more effective than face mask for positive pressure delivery in this population.
  - C. Triangular face masks have consistently been shown to have less air leak than circular masks in this population.
  - D. For face masks, the correct size should be determined by placing the bottom of the mask on the tip of the chin to cover the mouth and nose, but with the top of the mask not reaching the eyes.
  - E. The optimal "hold" of a face mask for preterm infants is to place in the correct position on the face, but actually not to hold it in place and let it lie there gently.
3. A female infant born at 27 weeks' gestational age is delivered vaginally and is handed to the pediatrics team after 60 seconds of delayed cord clamping. The infant has spontaneous respirations before cord clamping. At the radiant warmer, the infant is gasping and is determined to have inadequate respirations. The team initiates positive pressure ventilation. Which of the following parameters for initial support for this patient is most appropriate?
  - A. Inflation pressure of 30 cm H<sub>2</sub>O.
  - B. No positive end-expiratory pressure for the first few minutes.
  - C. A rate of 40 to 60 breaths/min.
  - D. Oxygen concentration of 60%.
  - E. Sustained inspiratory time of 10 seconds.

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4. The pediatrics team is preparing for the delivery of an infant at 27 weeks' gestational age for worsening preeclampsia in the mother. Several choices for delivering positive pressure ventilation are available to the team. Which of the following are advantages of a T-piece resuscitator over a self-inflating bag?
- A. The ability to accurately detect tidal volumes.
  - B. Several studies showing improved neurodevelopmental outcomes at 2 years of age.
  - C. Easier to deliver controlled positive pressure ventilation and continuous positive airway pressure.
  - D. Safeguard mechanism to ensure that an exact positive end-expiratory pressure never exceeds 5 mm H<sub>2</sub>O.
  - E. Capacity to work without a gas source.
5. A newborn infant delivered at 28 weeks' gestational age is receiving positive pressure ventilation by T-piece and mask at 2 minutes of age for apnea and heart rate of 60 beats/min. Which of the following is the best indicator of the effectiveness of positive pressure ventilation?
- A. A rising heart rate.
  - B. Increasing pink color of the extremities.
  - C. Manometry pressures indicating a peak inspiratory pressure greater than 20 cm H<sub>2</sub>O.
  - D. Oxygen saturation reading greater than 90%.
  - E. Consistent positive end-expiratory pressure reading of 5 cm H<sub>2</sub>O.

# Noninvasive Ventilation in the Delivery Room for the Preterm Infant

Heather Weydig, Noorjahan Ali and Venkatakrishna Kakkilaya

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# Oxygen Therapy for Neonatal Resuscitation in the Delivery Room

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## Education Gaps

1. The evolving discussion on recommendations for oxygen therapy in the delivery room for term and preterm infants.
2. The adverse effects of both excessive oxygen exposure and inadequate oxygen supplementation in the neonate during delivery room resuscitation.
3. The need for more evidence-based recommendations on intermediate levels of oxygen concentration for initiating newborn delivery room resuscitation and the neurodevelopmental outcomes of neonates resuscitated with room air.

## Abstract

Oxygen is commonly used in the delivery room during neonatal resuscitation. The transition from intrauterine to extrauterine life is a challenge to newborns, and exposure to too much oxygen can cause an increase in oxidative stress. The goal of resuscitation is to achieve normal oxygen levels as quickly as possible while avoiding excessive oxygen exposure and preventing inadequate oxygen supplementation. Although it has been shown that room air resuscitation is as effective as using 100% oxygen, often preterm infants need some degree of oxygen supplementation. The ideal concentration of oxygen with which to initiate resuscitation is yet to be determined. Current delivery room resuscitation guidelines recommend the use of room air for term newborns and preterm newborns of greater than or equal to 35 weeks' gestation and the use of a fraction of inspired oxygen of 0.21 to 0.3 for preterm infants of less than 35 weeks' gestation. Further recommendations include titrating oxygen supplementation as needed to obtain goal saturations. However, there is no current consensus on an intermediate oxygen concentration to start resuscitation or goal range saturations for preterm and asphyxiated term infants.

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### ABBREVIATIONS

BPD	bronchopulmonary dysplasia
DR	delivery room
FiO <sub>2</sub>	fraction of inspired oxygen
FRC	functional residual capacity
HIE	hypoxic-ischemic encephalopathy
ILCOR	International Liaison Committee on Resuscitation
IVH	intraventricular hemorrhage
NRP	Neonatal Resuscitation Program
PDA	patent ductus arteriosus
PPV	positive pressure ventilation
PVR	pulmonary vascular resistance
ROSC	return of spontaneous circulation
SVR	systemic vascular resistance
TOTS	transitioning oxygen target system

## Objectives After completing this article, readers should be able to:

1. Describe the detrimental effects of excessive oxygen exposure and inadequate oxygen supplementation during delivery room resuscitation.

2. Explain the transition from intrauterine to extrauterine life in infants and the pathophysiology of oxygenation during this transition.
3. Explain the goal of achieving normal oxygen levels in the blood and the current recommendations for oxygen use, both initiation and titration, in the delivery room for both term and preterm infants.
4. Describe the knowledge gaps in the utilization of oxygen therapy in the delivery room and the future research needed to clarify these deficits.

## INTRODUCTION

Most neonatal resuscitations in the delivery room (DR) use oxygen administration, especially when additional respiratory support is required. However, researchers have debated about the appropriate amount of oxygen to use. Studies have shown that excessive use of supplemental oxygen and inadequate supplemental oxygen can both adversely affect the neurodevelopment of a term or preterm neonate. Therefore, the goal for oxygen use in neonatal DR resuscitation is to use the appropriate amount of supplemental oxygen to achieve normal oxygen levels in the blood. This article will review 1) the history of oxygen utilization in the DR; 2) the pathophysiology of oxygenation in intrauterine and extrauterine life; 3) methods to assess for adequate oxygenation in a neonate; 4) the goal of using the appropriate amount of oxygen, recommendations on the initial fraction of inspired oxygen ( $\text{FiO}_2$ ) in both term and preterm infants, titration guidelines; and 5) the underlying evidence to support these recommendations. Finally, this review will conclude with oxygen use during cardiopulmonary resuscitation, the importance of ventilation, knowledge gaps, and future research needed on oxygen use in the DR.

## HISTORY OF OXYGEN USE IN THE DR

Oxygen use in the DR has become a standard in neonatal resuscitation. Oxygen is commonly used in the DR to achieve normal oxygen content in the blood while avoiding excessive use of supplemental oxygen and inadequate supplemental oxygen, given that studies have shown that both of these scenarios can have negative consequences on the development of a newborn. Over the years, there has been a shift from the use of 100% oxygen to room air (21%). Currently, the health care providers in the DR are responsible for recognizing the neonate's oxygenation status and appropriately titrating the  $\text{FiO}_2$ . (1)(2) For the

past 200 years, resuscitation with 100% oxygen has been widely used during DR resuscitations because complications with extrauterine transition largely arise because of cardiopulmonary failure associated with inadequate oxygenation. (3) In 1964, studies demonstrated that positive pressure ventilation (PPV) with 21% oxygen was effective in resuscitating animal models with hypoxemia (ie, low oxygen content in the blood). (3) This finding led to the wide use of PPV in neonatal resuscitation, but the use of 21% oxygen was ignored. (4)

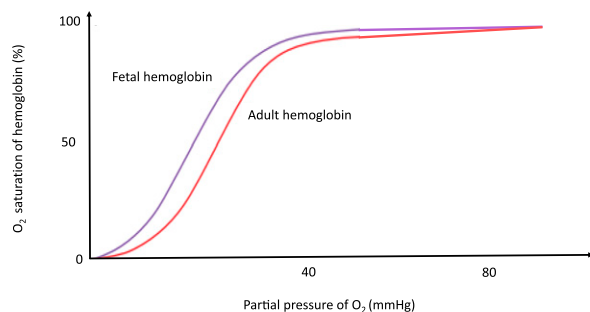
Since that time, many studies have found that resuscitation with room air was just as effective as 100% oxygen. The Resair 2 study, a prospective multicenter study of infants with birthweight greater than or equal to 1,000 g, showed that resuscitation with room air or 100% oxygen had similar outcomes including mortality rates, rates of hypoxic-ischemic encephalopathy (HIE), heart rates, 5-minute Apgar scores, and time to first spontaneous breath. (5) Multiple systematic reviews and meta-analyses have shown that room air resuscitation is superior given that it may actually result in a lower mortality rate in term infants. (6)(7)(8) The advent of such studies has shifted the view on oxygen use in the DR. From 1992 to the present, there has been a dramatic shift in recommendations—from room air as an alternative method in resuscitation to a strong recommendation for room air resuscitation in 2015. In 1992, clinicians believed that brief exposure to pure oxygen was not detrimental. By 2000, there was not enough data to recommend less than 100%, but it was allowable to use room air if oxygen was not available. (9) Since then, many studies have described the adverse effects of oxygen, such as reactive oxygen species production, and studies showing room air with similar efficacy as pure oxygen. (6)(7)(8) Currently, the leading recommendation is to use room air, particularly for term infants, for initial resuscitation. (9) The remainder of this review will focus on the physiology and evidence for current recommendations of oxygen therapy in the DR for infants

with hypoxemia and infants who require cardiopulmonary resuscitation.

## OXYGEN PHYSIOLOGY: INTRAUTERINE TO EXTRAUTERINE LIFE

Oxygen is a vital component of aerobic metabolism and is necessary for cellular function. The fetus is able to tolerate a low oxygen environment while in utero. The mean  $P_{aO_2}$  in utero is 25 to 35 mm Hg (3.3–4.6 kPa) and within minutes of birth rises to 65 to 75 mm Hg (8.6–9.9 kPa). Despite the low oxygen environment, the infant is able to survive and grow given various physiologic mechanisms. (10) Fetal hemoglobin is able to bind oxygen more efficiently than adult hemoglobin. On the oxygen-hemoglobin dissociation curve, fetal hemoglobin shifts the curve to the left (Fig 1). This shift allows for more efficient affinity of fetal hemoglobin for oxygen in low oxygenated environments, such as the placenta. (11) Fetal cardiac output is almost 4 times higher than that of adults and allows more oxygen to be delivered to the fetus. (12) Higher hemoglobin concentration in the fetus permits more oxygen to be carried in the blood. In addition, fetal physiology causes better oxygenated blood from the umbilical vein/ductus venosus to preferentially shunt from the right atrium through the foramen ovale to exit the left side of the heart to supply the brain. (3)

Many physiologic changes must happen to allow for successful transition to extrauterine life. When the infant is born, fluid in the alveoli is absorbed and replaced with air. Before and during labor, an increase in catecholamines leads to the active resorption of sodium and liquid in the lung epithelium. With the first initial breath, a rise in transpulmonary pressure helps shift the alveolar fluid into the interstitium. (13)(14) The resulting lung expansion and increasing inspiratory pressure help to establish functional residual capacity (FRC), which also stimulates surfactant to maintain FRC. (15) As depicted in Fig 2, with the first breath



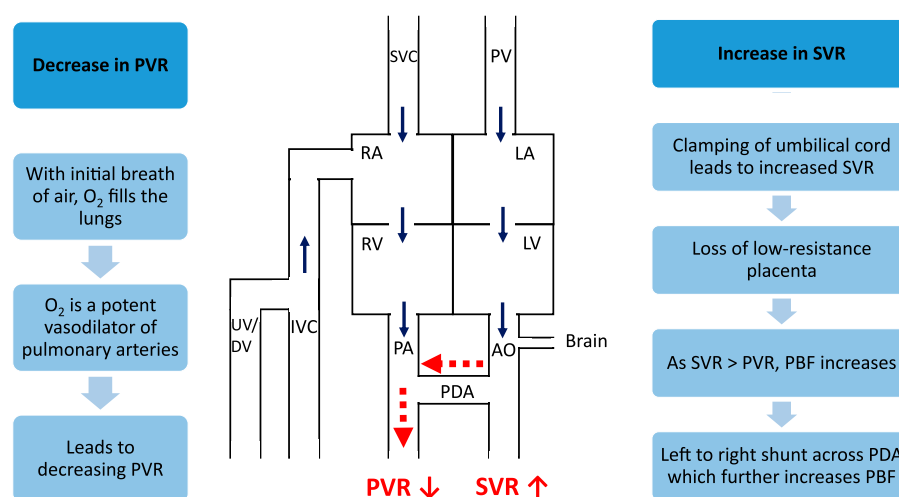
**Figure 1.** Fetal hemoglobin is able to bind oxygen more efficiently than adult hemoglobin. On the oxygen-hemoglobin dissociation curve, fetal hemoglobin shifts the curve to the left. (11)

of air, oxygen fills the lungs, causing pulmonary vascular resistance (PVR) to decrease. (16)(17) Clamping of the umbilical cord leads to an increase in systemic vascular resistance (SVR). As SVR increases and PVR decreases, pulmonary blood flow rises, leading to increased systemic oxygenation. (18) All of these changes contribute to a reversal of blood flow through the patent ductus arteriosus (PDA) (from right-to-left in utero, to left-to-right extrauterine) and its eventual closure. With increased pulmonary blood flow, left atrial pressure rises, leading to the closure of the foramen ovale.

## ASSESSMENT OF INFANT OXYGENATION

Given that the transition to extrauterine life involves a significant change in the neonate's oxygenation, accurate assessment of oxygenation is crucial. Visual assessment of an infant's oxygen saturation by clinicians has been shown to be highly inaccurate and an unreliable measurement of cyanosis. (19) In one study, clinicians were shown videos and asked to assess whether infants looked pink. The study showed that there was a very wide variation in actual oxygen saturations (from 10%–100%) when infants (mean gestational age, 31 weeks) were perceived as pink. (19) Studies such as these imply that unbiased measurement of oxygenation is a key component of resuscitation.

Pulse oximetry is a crucial part of DR resuscitation and is used routinely to help target oxygenation and facilitate efficacy of resuscitation when using PPV or supplemental oxygen. (1)(2) Pulse oximetry is used to help determine the oxygen saturation by calculating the percentage of oxygenated hemoglobin. Oxygenated hemoglobin (660 nm) absorbs light at a different wavelength than deoxygenated blood (910 nm). The oxygen saturation is calculated by the pulse oximetry device by computing a ratio between the 2 tissue absorptions. (20) The pulse oximetry probe should be placed on the infant before connecting it to the pulse oximetry device, as multiple studies have shown that time to pulse oximetry detection is faster when connected to the device after the probe is placed on the infant. (21)(22)(23) However, other studies have shown no difference in detection. (24) The probe should be placed on the right hand for a preductal saturation, which represents blood supplying the brain. (20) The International Liaison Committee on Resuscitation (ILCOR) and Neonatal Resuscitation Program (NRP) recommend that preductal saturations be measured by placing the probe on the right hand or wrist. (1)(2) In addition to the manufacturers' instructions to place the probe on the hand, it is appropriate to place it on the wrist as well. (24)(25)



**Figure 2.** With the first breath of air, oxygen, a potent vasodilator of pulmonary arteries, fills the lungs, causing pulmonary vascular resistance (PVR) to decrease. Concomitantly, clamping of the umbilical cord, which separates the infant from the low resistance placenta, leads to an increase in systemic vascular resistance (SVR). Clamping of the cord also blocks UV/DV flow to the right atrium. As SVR increases and PVR decreases, pulmonary blood flow (PBF) rises, leading to increasing systemic oxygenation. All of these changes contribute to a reversal of blood flow through the patent ductus arteriosus (PDA) (from left-to-right in utero, to left-to-right extrauterine) and its eventual closure. AO=aorta; DV=ductus venosus; IVC=inferior vena cava; LA= left atrium; LV=left ventricle; O<sub>2</sub>=oxygen; PA=pulmonary artery; PV=pulmonary vein; RA=right atrium; RV=right ventricle; SVC=superior vena cava; UV=umbilical vein. (13)(14)(15)(16)(17)(18)

One of the issues with pulse oximetry is the difficulty in getting an accurate measurement. Pulse oximetry has only been validated for saturations greater than 70% in healthy adult volunteers. Thus, there are no data or validation for readings below 70%. There is also difficulty in placing the probe properly on a moving infant, and it is important to avoid applying the probe too tightly. (26) Ambient light can also interfere with the accuracy of the pulse oximetry reading. (20) Therefore, applying an opaque wrap around the probe to protect it from ambient light will provide a more accurate read. Studies have shown that within 2 minutes of placing the probe, stable readings can be obtained. (27)(28) The pulse oximetry probe should not be placed on the foot because it will take longer to get a reading and will not represent preductal oxygen saturations. (29) The quality of the reading can be assessed by correlating heart rate from the pulse oximetry reading with the auscultated pulse.

## THE GOAL OF OXYGEN DELIVERY TO ACHIEVE NORMAL OXYGEN CONTENT

The goal of oxygen in the DR is to avoid excessive oxygen supplementation and avoid inadequate oxygen supplementation while achieving normoxemia (ie, normal oxygen content in the blood) as quickly as possible. Achieving this goal in a newborn who is transitioning from intrauterine to extrauterine life is an oxidative challenge. (30) Transitioning from a relatively physiologic hypoxemic environment in utero to a potentially high blood oxygen content after birth

may cause free radical and oxidative stress in the newborn. In an effort to avoid hypoxemia, the use of 100% oxygen can inadvertently lead to excessive oxygen exposure, which can have detrimental effects. Hypoxic tissue that is exposed to a high concentration of oxygen can result in a reperfusion injury with increased free radical damage and oxidative stress. (31) Reactive oxygen species are highly unstable molecules that are derived from oxygen. Free radicals can create a chain reaction that disrupts essential cellular structures such as proteins, nucleic acids, and lipids when trying to achieve stability by aggregating with other molecules in the hopes of acquiring electrons. (32) Even exposures to 100% oxygen for less than 3 minutes can cause an increase in reactive oxygen species. (33) Studies trying to achieve the NRP target oxygenation with a lower oxygen strategy in preterm neonates showed decreased oxidative stress, defined as a higher oxidative balance ratio measuring antioxidant potential over total hydroperoxide, and lower respiratory morbidities, such as ventilator days and bronchopulmonary dysplasia (BPD). (34) In piglet models, there is a dose-dependent increase in oxidation markers with increased FiO<sub>2</sub> as measured by oxidation of DNA and phenylalanine in urine. (35) In sheep models, 100% oxygen resuscitation after intrauterine asphyxia induced higher oxygen tension in brain tissue. (33)

Multiple clinical studies have shown a lower incidence of BPD in preterm infants with the use of low oxygen in DR resuscitation. (34)(36)(37) Animals exposed to excessive amounts of oxygen have pathophysiologic findings that

are similar to BPD. (38)(39) The production of proinflammatory cytokines from exposure to high levels of oxygen has been shown to lead to lung injury and reprogramming of lung development. (40)(41)(42) High oxygen exposure can cause pulmonary, neurologic, cardiac, and renal damage immediately after resuscitation. There is some evidence of a higher risk for pediatric malignancy. (43)(44) Studies have shown that infants with perinatal acidemia who were exposed to high amounts of oxygen had a higher incidence of HIE. (30) In animal models, the neuroprotective effects of hypothermia were counteracted in infants resuscitated with 100% oxygen. (45) High oxygen exposure in animal models after hypoxic-ischemic brain injury showed impairment in recovery and a proinflammatory cerebral response. (46)(47)(48)

A meta-analysis with multiple randomized or quasi-randomized studies measuring the effects of resuscitation with 21% versus 100% oxygen showed a significant reduction in neonatal mortality and morbidity with room air resuscitation; infants of all gestational ages were included in this study. (8) However, another recent meta-analysis comparing preterm infants resuscitated in the DR with higher ( $\text{FiO}_2 \geq 0.6$ ) versus lower ( $\text{FiO}_2 \leq 0.3$ ) oxygen concentrations showed no significant difference in mortality. (49) This study also had some conflicting data between masked and unmasked studies leading to the conclusion that larger studies are needed before definitive oxygen recommendations can be made. (49) Randomized clinical trials did not show any advantage to using 100% oxygen in moderately asphyxiated term neonates. (50)(51) In contrast, term infants resuscitated with room air did better in the immediate setting as evaluated by Apgar scores and onset of spontaneous cry. (50) However, studies show that low oxygen content in tissues can also lead to decreased tissue perfusion, resulting in anaerobic metabolism and metabolic acidosis. Further, the “oxygen paradox” is defined as the reperfusion injury that results from oxygen supplementation after a period of tissue hypoxia. (52) Retrospective studies have shown that high oxygen exposure immediately after birth in asphyxiated infants with severe perinatal acidemia was associated with a higher incidence of HIE. (30)(52) Given the adverse effects of high oxygen exposure and hypoxia, the goal of oxygen use is, therefore, to achieve normal oxygen content in the blood and tissues during DR resuscitation.

## INITIAL $\text{FiO}_2$ FOR TERM INFANTS AND LATE PRETERM INFANTS OF $\geq 35$ WEEKS' GESTATION AND INFANT OUTCOMES

Pure oxygen was routinely used for neonatal resuscitation until around 2010. As previously discussed, studies showing

the detrimental effects of high oxygen exposure in animal models quickly accumulated, providing evidence against this practice. (33)(35)(48) Follow-up studies from the Resair trial showed no significant differences between using room air versus  $\text{FiO}_2$  of 1.0 during resuscitation of infants with birth-weight greater than or equal to 1,000 g when assessing for somatic growth or neurologic outcomes at age 18 to 24 months. (53) Systematic review of randomized and quasi-randomized studies did not show any disadvantage to initiating resuscitation with room air. (54) Term infants resuscitated with room air had better Apgar scores, improved time to initial cry, and sustained respiratory patterns. (50)(51)(55) Systematic reviews and meta-analyses alluded to lower mortality rates in term infants resuscitated with room air. (6) These studies, however, had many limitations noted by the authors. First, some studies were quasi-randomized. Second, many deliveries were started at  $\text{FiO}_2$  of 0.21 and then increased to  $\text{FiO}_2$  of 1 when needed during resuscitation, complicating data analysis. Last, some studies were done in developing countries without the same resources. The question remains if these results can be applied more broadly. Also, long-term neurodevelopmental assessment for infants resuscitated with room air and 100% oxygen did not follow strict assessment criteria, and many subjects were lost to follow-up. (7)(56)

There has been additional concern that starting resuscitation at lower oxygen levels would lead to an inadequate decrease in PVR. An animal study by Lakshminrusimha et al addressed this concern and showed that PVR dropped faster in 100% oxygen-resuscitated lambs at 1 minute, but there was no difference 2 to 30 minutes after resuscitation. (57) In addition, pulmonary arteries showed signs of increased superoxide anion staining in lambs resuscitated with 100% oxygen. (57) Further, studies showed that resuscitation with 100% oxygen did not decrease PVR more effectively than room air but did impair response to nitric oxide treatment in lambs with induced persistent pulmonary hypertension. (58)

## Recommendations

NRP and ILCOR recommend that newborn DR resuscitation should be initiated with room air for term or preterm infants of gestations greater than or equal to 35 weeks. Oxygen can then be titrated using a blender with guidance from pulse oximetry findings, with a goal of preductal oxygen saturations approximating the interquartile range (25%–75%) in healthy term infants born via vaginal birth. (1)(2) Thus, supplemental oxygen using a blender should be readily available. There is a lack of data, however, on using intermediate oxygen concentrations (21%–100%) for initial resuscitation at this time for term infants and late preterm



infants of gestations greater than or equal to 35 weeks. Currently, there is also a lack of data on long-term morbidity and mortality for term infants and late preterm infants of gestations greater than or equal to 35 weeks who are resuscitated with any level of oxygen.

**Oxygen Saturation Targets During DR Resuscitation of Term Infants**

Given the clear benefits of maintaining normal oxygen content in the blood, the next issue facing DR practitioners is how to define normal oxygen content during the transition after birth. A cohort study by Dawson and Morley published reference ranges for oxygen saturations for the first 10 minutes after birth in 468 term, healthy newborns not requiring resuscitation. (59) Mariani et al also measured preductal oxygen saturations in 110 term healthy newborns born via vaginal delivery at sea level and who had spontaneous respirations at birth. The researchers found that preductal oxygen saturation levels did not exceed 90% until after 5 minutes of age. (60) The researchers also estimated the oxygen saturation interquartile range for these infants. The NRP currently uses interquartile ranges (25%–75%) estimated from these studies as the target oxygen saturation for neonates in the first 10 minutes after birth (Table). (61) This recommendation is based on expert opinion and the desire to avoid excessive or inadequate amounts of supplemental oxygen during neonatal DR resuscitation. Currently, there are no large randomized controlled trials that compare different goal saturations in the first 10 minutes after birth. The clinician will need to use his or her best clinical judgment to determine how rapidly or often to titrate oxygen to achieve these goal saturations. (62)

With the advent of delayed cord clamping in the DR, studies have been undertaken to determine the effects of

delayed cord clamping on oxygen saturations after birth. These preliminary studies show that oxygen saturation levels are higher in the first 10 minutes after birth and have a slower rate of rise compared with the reference range defined by Smit and colleagues. (63) The standard reference range could be used for this population of infants, but there are no recommended target oxygen saturation curves for neonates with delayed cord clamping. More studies are needed in this arena. (62)

**INITIAL FiO<sub>2</sub> FOR PRETERM INFANTS OF <35 WEEKS' GESTATION AND INFANT OUTCOMES**

Before 2010, 100% oxygen was used for initial newborn resuscitation of preterm infants. However, many studies showed evidence of increased oxidative stress and potential organ damage with resuscitation using high amounts of oxygen. (32)(35)(46) Initial studies showed that using a limited oxygen strategy was feasible with preterm infants and decreased exposure to oxidative stress. (34) Many studies, however, show that most preterm infants require some supplemental oxygen during resuscitation. (34)(36) In these studies, both the high (FiO<sub>2</sub> of 1) and limited (FiO<sub>2</sub> of 0.21) oxygen groups ended up with an FiO<sub>2</sub> of 0.3 to maintain goal saturations (extrapolated from full-term infants) at the time of stabilization. (34)(36) Further, trials have shown that resuscitation with 21% oxygen had a high failure rate, as defined by heart rate lower than 100 beats/min for more than 30 seconds. (64)(65) A meta-analysis of 504 infants conducted by Oei et al analyzed 8 randomized controlled trials and showed no overall risk differences between the 2 groups (low FiO<sub>2</sub> of ≤0.3 and high FiO<sub>2</sub> of ≥0.6) with regard to the main outcome measures of death, BPD, retinopathy of prematurity, intraventricular hemorrhage (IVH) grades 3 and 4, and PDA. (49) Nevertheless, the risk of death had opposing results for masked and unmasked studies, confirming the need for larger studies. (49) Oei et al also conducted the largest randomized clinical trial comparing room air with 100% oxygen in preterm infants. (66) The trial was initially powered to assess for death and developmental impairment at 2 years of age but was stopped early because of recruitment difficulties. In the end, the study was underpowered. (66) Nonetheless, the authors found that preterm infants who were resuscitated with room air required less respiratory support and less time on supplemental oxygen, and the incidence of PDA was lower. (66) These data were added to their previous meta-analysis of 504 infants. The addition of these new data showed no difference in mortality between the 2 groups. (49)(66) In a subgroup analysis of infants born before 28 weeks, 22% of

**TABLE. Preductal Oxygen Saturation Target Range for Term Neonates After Birth (61)**

1 min	60%–65%
2 min	65%–70%
3 min	70%–75%
4 min	75%–80%
5 min	80%–85%
10 min	85%–95%

infants in the room air group died compared with 6% in 100% oxygen. It is worth noting, however, that this group was severely underpowered, and the author stated that given the small sample size, a single death in either group would have altered the data. (66)

In a randomized controlled study, there was no difference in neurodevelopmental outcome at 24 months and survival between the lower ( $\text{FiO}_2 \leq 0.3$ ) and higher ( $\text{FiO}_2 \geq 0.6$ ) oxygen supplementation preterm infant groups. (67) In fact, a study showed that a low oxygen strategy was associated with improved neurodevelopmental outcome and improved BPD with no changes to mortality in infants less than 29 weeks. (37) Two studies from the Canadian Neonatal Network have shown differing outcomes. (68)(69) In the first study, there was a higher incidence of death and IVH grade 3 or 4 in preterm infants when initially resuscitated with room air. (68) A subsequent study from the same group did not show any significant differences in incidence of death or neurodevelopmental impairment at follow-up at 18 to 21 months of age. The study showed that preterm infants resuscitated with 100% oxygen had higher odds of developing severe neurodevelopmental impairments. (69)

### Recommendations

ILCOR and NRP recommend initiating resuscitation with low oxygen concentration between 21% and 30% for preterm infants of less than 35 weeks' gestation. This strong recommendation is based on moderate quality evidence. This recommendation emphasizes the point of not exposing infants to excessive oxygen without clinical benefits.

### Oxygen Saturation Targets During DR Resuscitation of Preterm Infants

Many studies have extrapolated from data on full-term infants and shown that preterm infants are not able to remain within target oxygen saturations within the first few minutes after birth and require supplementary oxygen. (70) When resuscitated with 21% oxygen, preterm infants have an increased likelihood of not reaching target oxygen saturations. (64)(65) On the other hand, these trials also showed a high likelihood of exceeding the target oxygen saturation when initiating resuscitation with higher levels of oxygen between 60% and 100%. (34)(65)(70)(71)(72) Other methods of tracking oxygen, such as the transitioning oxygen target system (TOTS), have been developed to enable newborn resuscitations to stay within target oxygen saturations. (28) TOTS graphically plots the infant's oxygen saturation in relation to the 10th and 50th percentile target oxygen curves. This allows the clinician in the DR to

visualize the infant's status on the curve and adjust the  $\text{FiO}_2$  accordingly. When using TOTS, preterm infants were maintained within the target saturation for longer than those infants not evaluated with TOTS. (28)

There are many issues in the application of NRP-recommended target oxygen saturation in preterm infants, given that the data are derived from healthy, term infants not requiring resuscitation. (62) The question lies in the fact that preterm infants have different lung pathophysiology, such as surfactant deficiency and immature antioxidant defense systems, compared with term, healthy infants. Thus, preterm infants may require different oxygen levels than healthy, term infants. Fortunately, there are large randomized controlled trials currently in process that could help us further answer this question. (73)(74)

### USE OF $\text{FiO}_2$ 1.0 DURING CARDIOPULMONARY RESUSCITATION IN THE DR

According to NRP guidelines, if the infant's heart rate remains below 60 beats/min despite adequate ventilation, chest compressions should be started. (1)(2) During this time,  $\text{FiO}_2$  should be increased to 1.0. (61) The reasoning behind this recommendation is that by the time a newborn needs chest compressions, adequate ventilation steps should have been completed with room air to achieve return of spontaneous circulation (ROSC). Currently, there are no human studies to support or contradict this recommendation. Further, animal studies have not shown any advantages to using 100% oxygen in achieving ROSC or survival. (33)(75)(76)(77)(78)(79)(80) Data on the neurologic outcome and oxidative injury are inconclusive in these studies. This recommendation of the use of 100% oxygen during cardiopulmonary resuscitation in the DR therefore is based on best clinical practice and expert opinion. Until further studies and knowledge are available, it is reasonable to provide 100% oxygen during chest compressions. Once ROSC is achieved and the infant's heart rate is within appropriate range, oxygen should be weaned per target oxygen saturations to avoid excessive supplemental oxygen.

### IMPORTANCE OF VENTILATION DURING CARDIOPULMONARY RESUSCITATION IN THE DR

NRP contains multiple steps that include newborn assessment and implementation of interventions to ensure a smooth transition for the newborn from intrauterine to extrauterine life. It is crucial to assess for adequate respiratory effort and a normal heart rate, which are indicators

of adequate oxygenation. Adequate ventilation must be achieved to have adequate oxygenation. The NRP algorithm states that ventilation is the primary intervention in newborns with bradycardia in the DR, and corrective steps should be taken to achieve ventilation before initiating compressions or intubation. (61) Cardiac output is defined as stroke volume multiplied by heart rate. Therefore, bradycardia will lead to reduced cardiac output that would then cause inadequate oxygen delivery to organs and tissues. Hence, improvement from bradycardia to a regular heart rate is a good indicator of proper ventilation and oxygenation.

## KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

### What Are the Effects of Starting Resuscitation at Intermediate Levels of Oxygen?

Data have shown that 100% oxygen has many detrimental effects on the newborn. However, we do not know the optimal oxygen concentration at which to start resuscitation for preterm or asphyxiated term infants. Starting resuscitation at room air often has failed, requiring an upward titration of  $\text{FiO}_2$ . More studies are needed using intermediate levels of oxygen for initial resuscitation before firm recommendations can be made for the best initial  $\text{FiO}_2$  for preterm or asphyxiated infants requiring resuscitation.

### Can the Target Oxygen Saturations Recommended by the NRP and ILCOR be Extrapolated to Asphyxiated Infants?

Target oxygen saturations recommended by the NRP and ILCOR are based on studies of healthy, term infants who did not require any resuscitation. The question remains if this data set can be applied to severely asphyxiated infants. Further, it is unclear if target oxygen saturations are the same for severely asphyxiated infants and mildly asphyxiated infants. More trials are needed to stratify the severely asphyxiated group.

### Can the Target Oxygen Saturations Recommended by the NRP and ILCOR be Extrapolated to Preterm Infants?

As mentioned previously, preterm infants have different lung pathophysiology, such as surfactant deficiency, compared with term healthy infants. In addition, the brains of preterm infants have low antioxidant levels, excess free iron secondary to IVH, and increased vulnerability of their preoligodendrocytes to oxidative stress. (81) Therefore, the

brains of preterm infants are more susceptible to the adverse effects of excessive supplemental oxygen compared with term infants. Preterm infants may thus need different target oxygen saturation goals compared with healthy, term infants.

### What Are the Long-Term Neurologic Consequences of Using Room Air for Resuscitation in Term and Preterm Infants?

Studies on the long-term outcomes of resuscitating infants at higher or lower levels of oxygen are limited. Data on whether or not there is any long-term neurologic consequence of infants resuscitated with room air have also been conflicting. Larger scale studies are needed to elucidate detailed follow-up, including neurodevelopmental outcome scores, at 18 to 24 months of age.

## CONCLUSION

The current goal of oxygen therapy in the DR is to achieve adequate oxygenation of the newborn without exposure to excessive or inadequate supplemental oxygen because these can have detrimental consequences. The present NRP recommendation is to start resuscitation with  $\text{FiO}_2$  of 0.21 for infants of gestations greater than or equal to 35 weeks and  $\text{FiO}_2$  of 0.21 to 0.3 for infants of gestations less than 35 weeks. Oxygen should be titrated to help maintain recommended target oxygen saturations (which are only established for term, healthy neonates). However, long-term outcomes of this approach are still unclear. Further, data evaluating intermediate levels of supplemental oxygen with which to initiate resuscitation are limited. The effects of mortality and morbidity in applying the recommended target oxygen saturations to preterm and asphyxiated term infants are also uncertain. More trials therefore are needed to evaluate the optimal initial oxygen concentration and the most effective level of target oxygen saturation during DR resuscitation in these vulnerable populations.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know indications for and proper administration of supplemental oxygen immediately after birth.

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1. You are attending the delivery of a neonate at 39 weeks' gestation. The obstetric team has called the pediatrics team because of concern for category 3 fetal heart tracing. The infant appears limp at birth and has no respiratory effort. The cord is clamped and the infant is brought to the radiant warmer for resuscitation. Which of the following is the most appropriate initial oxygen concentration for resuscitation?
  - A. 19%.
  - B. 21%.
  - C. Between 21% and 30%.
  - D. 40%.
  - E. 100%.
2. The fetus tolerates a relatively low oxygen environment in utero, with the mean  $P_{aO_2}$  in utero being 25 to 35 mm Hg. Which of the following is a physiologic mechanism that facilitates this tolerance?
  - A. Fetal hemoglobin binds oxygen more efficiently than adult hemoglobin, because fetal hemoglobin shifts the oxygen-hemoglobin curve to the left.
  - B. The fetus reduces energy consumption by forcing itself into a relatively anemic state throughout all 3 trimesters.
  - C. Cardiac energy consumption is selectively reduced by maintaining cardiac output at half the level produced by adults.
  - D. Cardiac physiology in the fetus leads to blood preferentially being directed toward the heart only, because this is the only vital organ during fetal life.
  - E. The fetal heart uses nitrogen and calcium via anaerobic metabolism to convert maternal nutrients into adenosine triphosphate.
3. A newborn term infant has spontaneous cry at birth after 3 hours of labor and a normal spontaneous vaginal delivery. The umbilical cord is clamped at 1 minute of age. The infant is mildly cyanotic at birth and gradually transitions to pink color. On assessment at 5 minutes of age, there are equal, coarse-sounding breath sounds on physical examination with no signs of distress. Which of the following statements that concern the transition to extrauterine life is correct?
  - A. Before and during labor, an increase in catecholamines will lead to active resorption of sodium and liquid in the lung epithelium.
  - B. An increase in fluid shifting into the pulmonary space increases the functional residual capacity volume before the fluid shifts outward primarily via the trachea.
  - C. Increasing inspiratory pressures lead to stretching of the alveolar XP cells that react within seconds to secrete surfactant.
  - D. Clamping of the umbilical cord leads to a decrease in systemic vascular resistance, which leads to fluid shifting away from the pulmonary vasculature and the lungs.
  - E. A sudden drop in atrial pressure because of oxygen signaling leads to closure of the ductus arteriosus and foramen ovale.
4. A pediatrics team is called to a scheduled cesarean delivery for breech presentation at term gestation. As the team prepares for the delivery and potential for resuscitation, roles are assigned, including for assessment of the neonate's oxygenation. If the neonate receives resuscitation, which of the following would be the most appropriate method to assess the oxygenation status in the first few minutes after birth and during ongoing resuscitation?
  - A. Visual appearance of the skin, including the mucous membranes.
  - B. Rapid umbilical arterial catheterization and blood gas measurement.
  - C. Continued use of fetal scalp electrode connected to oxygenation meter.
  - D. Pulse oximetry device with probe placed on the right hand.
  - E. Near-infrared spectroscopy of the cerebral vessels.

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5. The pediatrics team is preparing for the delivery of an infant at 26 weeks' gestation. Which of the following may be a benefit or adverse consequence of using 100% oxygen instead of a lower concentration?
- A. Increased free radical and oxidative stress, which may lead to disruption of essential cellular structures such as proteins, nucleic acids, and lipids.
  - B. Lower likelihood of later development of bronchopulmonary dysplasia.
  - C. Lower likelihood of developing hypoxic-ischemic encephalopathy.
  - D. Reduction in risk of mortality.
  - E. Higher Apgar scores.

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# Caveats of Cooling: Available Evidence and Ongoing Investigations of Therapeutic Hypothermia

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## Education Gap

Therapeutic hypothermia (TH) initiated within the first 6 hours after birth is the recommended treatment for neonates born at 36 weeks or greater gestational age diagnosed with moderate to severe hypoxic-ischemic encephalopathy (HIE). Results of multiple randomized controlled trials demonstrated that TH reduces morbidity and mortality in this population. However, 40% to 55% of neonates with HIE treated with TH will still suffer substantial neurologic disability in the future or will die. Ongoing areas of investigation are focused on whether TH confers benefit to other neonatal populations, when to discontinue the treatment, neurologic monitoring and sedation with TH, and type of neuroimaging needed after treatment.

## Abstract

Therapeutic hypothermia (TH) mitigates the long-term effects of neuronal excitotoxicity and cell death seen in hypoxic-ischemic encephalopathy (HIE). It remains the most evidence-based therapy for HIE, but it is not without clinical controversy. The literature abounds with questions, such as "When should we start cooling—as early as the delivery room?" "Given the efficacy of TH for moderate to severe HIE when started within 6 hours of birth, can we expand the therapy to infants with mild HIE?" "What should the target temperature be?" "What is the optimal duration of treatment?" "Is early discontinuation acceptable if the examination findings normalize?" These questions about TH, its incomplete neurologic rescue, and variations in the delivery of this therapy have prompted this review. This article summarizes changing procedural considerations for TH, the level of neuromonitoring available, the use of sedation, and considerations for neuroimaging during and after TH.

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### ABBREVIATIONS

aEEG	amplitude-integrated electroencephalography
EEG	electroencephalography
GA	gestational age
HIE	hypoxic-ischemic encephalopathy
MRI	magnetic resonance imaging
NIRS	near-infrared spectroscopy
RCT	randomized controlled trial
rSO <sub>2</sub>	regional mixed venous saturation
TH	therapeutic hypothermia
vEEG	video electroencephalography

## Objectives After completing this article, readers should be able to:

1. Describe rates of morbidity and mortality among infants with moderate to severe hypoxic-ischemic encephalopathy (HIE) who are treated with therapeutic hypothermia (TH).

2. Explore current recommendations for TH and HIE and describe recent and ongoing clinical investigations of TH in novel populations.
3. Review neuromonitoring and neuroimaging strategies used in conjunction with TH.

## INTRODUCTION

In developed countries such as the United States, the incidence of hypoxic-ischemic encephalopathy (HIE) is 3 to 5 in 1,000 live births. (1) This number increases by 10-fold when infants are cared for in resource-limited settings without access to advanced technology. (2) The pathophysiology of HIE is complex. Many factors affect the extent of damage caused by hypoxic injury. (3) An initial insult occurs when the brain is deprived of oxygen. The severity of the injury depends on the timing of the injury before delivery, the infant's gestational age (GA), and the adequacy of cerebral blood flow when ischemia occurs. The ischemic event influences the integrity of preexisting neuronal cell types in the brain. (4) When oxygen delivery to neurons is impaired, adenosine triphosphate production is immediately disrupted, leading to rising lactate, acidosis, and activation of calcium entry into cells. Calcium influx stimulates N-methyl-D-aspartate receptors in neuronal cells. (5) All these events happen within minutes, making this an extremely brief and difficult period to target using medical therapies. Following this initial insult is a latency or reperfusion period. (5) During this time, cell damage is mediated by proinflammatory signals, an imbalance of excitatory and inhibitory neurotransmitter release, and oxidative stress, which in combination, culminate in eventual cell necrosis and apoptosis. (6)

Therapeutic hypothermia (TH) is currently the only proven clinical therapy to ameliorate brain injury for neonates with moderate to severe HIE. TH confers a 25% risk reduction in the primary outcome of disability or death in infants of more than 35 weeks' GA who are cooled within 6 hours after delivery. (7) The most recent Cochrane review from 2013 included 11 randomized controlled trials (RCTs) asserting the benefits of TH for infants with HIE. (1) Current recommendations from the American Academy of Pediatrics state that infants receiving TH should have the following eligibility criteria based on these RCTs: a history of perinatal insult, GA greater than 35 weeks, be identified within 6 hours after birth, Apgar scores less than or equal to 5 at 10 minutes after birth, need for continued resuscitation at 10 minutes after birth, pH less than 7.00 or

base deficit greater than or equal to 16 on cord blood samples obtained within 60 minutes after birth, and moderate to severe encephalopathy on clinical examination with or without seizures (Table 1). (8) It is also recommended that infants be transferred to a center that can provide comprehensive critical care and follow-up for these infants. (8)

Despite evidence that TH reduces the risk of death and neurodevelopmental disability, the benefit is not universal for all patients. The incidence of death and disability after the use of this therapy is still high, estimated at approximately 40% to 55%. (8)(9) This persistent poor overall prognosis for HIE has led to questions on how to optimize the use of TH, including the qualifications for therapy, timing, depth/temperature, and length of cooling. This article will review these ongoing investigations in cooling, and review the recommended degree of neuromonitoring, amount of sedation, and neuroimaging during and after treatment.

## CONTROVERSIES IN COOLING

### Cooling of Infants with Mild HIE

Current guidelines for TH require that an infant meet criteria on neurologic examination for moderate or severe hypoxic injury (Table 2). This determination is based on a time-sensitive provider assessment at the time of delivery and within the first 6 hours after birth. Increasingly, providers have been extending the use of TH to include infants who do not have a severe enough clinical picture to qualify for entry into a research study. This trend toward inclusivity is likely the result of the perceived strong evidence for neuroprotection after TH, with relatively few clinically important risks. Infants noted to have mild encephalopathy were initially excluded from earlier studies, but recent retrospective evaluations of brain injury in this population has raised the question of whether TH would be beneficial in these infants. (10) A study of infants with mild HIE (defined as having  $>1$  abnormality using modified Sarnat staging but who did not meet cooling criteria) found that at 18 to 22 months, 16% of infants were eventually diagnosed with disability. (11) While this is less than that seen for moderate to severe encephalopathy, the concern for adverse outcomes



TABLE 1. **Current American Academy of Pediatrics Recommendations for Cooling**

CLINICAL CONSIDERATION	THRESHOLD FOR COOLING
Perinatal insult	Convincing story of ischemic injury during delivery (subjective)
Gestational age at birth	>35 weeks
Age at time of cooling	<6 hours after birth
Apgar scores	<5 at 10 minutes after birth
Resuscitation efforts	Required at >10 minutes after birth
Cord blood samples (or blood gas samples obtained within 60 minutes of age)	pH <7.00, base deficit >16
Neurologic examination	Moderate to severe encephalopathy, as defined by Sarnat staging
Seizures	Presence of seizures (of note, this is not required for cooling but would prompt the initiation if seen at <6 hours of age)

in this population has created a shift in therapeutic eligibility, with more centers electing for treatment with TH in mild HIE cases. (10) The initial challenge with extending the boundaries of eligible infants for TH is defining mild HIE. There is currently no uniform definition for infants in this category, because it is difficult to predict who will worsen clinically after perinatal injury. (10) Uniform definitions of mild HIE and clinical trials in this population are needed to support this increasingly popular practice, to better weigh the risk-benefit ratios for treatment.

#### TH for Premature Infants

Aside from treating mild HIE, ongoing studies of preterm infants with HIE who are receiving TH might broaden the recipient patient population even further. Complicating this extension of therapy is the knowledge that HIE in premature infants has a unique pathophysiology involving both grey and white matter. In addition, cold stress in premature infants is a known phenomenon with the potential for increased risk of mortality. (12) The specific risks of intracranial hemorrhage, difficulty with respiratory management, and increased risk for nosocomial infection have made researchers hesitant to offer TH in infants of less than 31 weeks' GA. (12) Despite the concern for more adverse events, trials for late preterm infants are beginning to enroll infants born at 33 to 35 weeks' GA. (8) Among 1,505 infants enrolled in RCTs of TH, only 1 clinical trial included infants of less than 36 weeks' GA at birth. (1) The ICE Trial accepted infants for study who were greater than or equal to 35 weeks' GA and greater than 2 kg at birth, for a total enrollment of 542 infants; the study does not specify the

number of infants who were born at 35 weeks' GA. (13) The study findings were consistent with other international trials on the advantages of cooling, but most enrolled infants were over 36 weeks' gestation and so the generalizability of this finding to infants at 35 weeks' GA is unclear. Given that this was the only study to include infants who were born at 35 to 36 weeks' GA, it is difficult to draw conclusions about how younger infants will tolerate cooling. More data are needed before TH is recommended for infants of younger gestational ages.

#### Timing of Cooling Therapy: When to Start and Stop

Recommendations for the timing of TH are based on a majority of published clinical trials that enrolled only infants in whom TH was initiated within the first 6 hours after birth. Yet, there is a subset of infants who are diagnosed with HIE after this period, or who arrive at facilities that provide TH later than 6 hours after birth. These circumstances prompted the National Institute of Child Health and Human Development Neonatal Research Network to conduct the "late hypothermia" trial to determine the impact of initiating TH between 6 and 24 hours after birth. In the recently published results, outcomes seem similar when comparing a primary outcome of death or disability between those randomized to late hypothermia and controls who did not receive TH. Therefore, the findings from this study reinforce the importance of early identification of infants with HIE as well as beginning treatment within 6 hours after birth. (14) As a corollary, very early initiation of hypothermia (during resuscitation) remains in question. Empirically, some providers discontinue the warmer in the

**TABLE 2. Current Recommendations and Ongoing Clinical Investigations**

CURRENT CONTROVERSIES	CURRENT EVIDENCE	RECOMMENDATIONS
Treatment of mild HIE	No RCT with a large cohort of these infants, though found in small percentages in certain trials (eg, ICE trial)	No recommendation to cool neonates with mild HIE
Cooling premature infants (<36 weeks' GA)	Concern for neurodevelopment, cold stress, increased risk of mortality	No recommendation for cooling neonates with GA <36 weeks
Late cooling (initiation >6 hours after birth) for HIE	No evidence to support cooling initiated at >6 hours after birth improves outcomes	No recommendation to initiate cooling >6 hours after birth
Initiation of cooling in the DR	No evidence to support initiation for cooling in the DR	No recommendation for initiation of cooling in the DR
Early discontinuation of cooling (ie, before 72 hours)	Concern for poorer outcomes when therapy is discontinued early because of improved clinical examination findings, normal EEG, or no changes on brain imaging	Recommendation is to cool for 72 hours
Extension of cooling period	Increased risk of arrhythmias, anuria, and longer hospitalizations	Recommendation is to cool for 72 hours
Lower temperature for cooling	Risk of increased inhaled nitric oxide use and ECMO with lower target temperatures	Target temperatures are set at 92.3°F–94.1°F (33.5°C–34.5°C)
Neuromonitoring	Risk of seizures, need for EEG	Monitoring should be initiated using aEEG, conventional EEG, or vEEG No recommendation for use of NIRS and target rSO <sub>2</sub>
Sedation	Concerns about impact of cooling on drug metabolism	Varied clinical practices, no RCTs looking at impact (positive or negative) on outcomes
Neuroimaging	Needed to help establish degree of cerebral injury and prognosticate for families	Infant should receive care at a center with MRI capabilities; MRI should be obtained 7–21 days after injury to capture cytotoxic edema on DWI Increasing use of cranial US including dynamic measurements of flow, but US still unreliable to identify HIE

aEEG=amplitude-integrated electroencephalography; DR=delivery room; DWI=diffusion-weighted imaging; ECMO=extracorporeal membrane oxygenation; EEG=electroencephalography; GA=gestational age; HIE=hypoxic-ischemic encephalopathy; MRI=magnetic resonance imaging; NIRS=near-infrared spectroscopy; RCT=randomized controlled trial; rSO<sub>2</sub>=regional mixed venous saturation; TH=therapeutic hypothermia; US=ultrasonography; vEEG=video electroencephalography.

delivery room during resuscitation of an infant with suspected HIE. Although there are data to suggest, particularly in animal models, that initiation of cooling in postnatal hours 1 to 3 is more efficacious than in hours 3 to 6, (10) initiating hypothermia while establishing cardiorespiratory stability may be ill-advised. Promotion of circulation is a priority in resuscitation and may be compromised by hypothermia. More information is needed to know how quickly cooling should be implemented, and no data exist to suggest that passive cooling in the delivery room confers any benefit.

In addition, the aforementioned trend of providing TH to infants with mild HIE has raised questions regarding the benefits and risks of early discontinuation of cooling. No

randomized trials have compared a shorter duration of TH to the standard 72 hours of treatment. In observational retrospective studies, early discontinuation of TH based on clinical impressions may not offer full neuroprotection to infants. (15) In these studies, TH was discontinued early largely because of normalization of electroencephalography (EEG) patterns and lack of evidence of damage on cerebral imaging. However, later imaging has revealed ischemic changes, and developmental scoring after 2 years has shown potential for delays, with 24% of infants who received early discontinuation having neurodevelopmental issues. (15) Use of hypothermia for 72 hours is superior compared with 48 hours seen in sheep models. (16) It remains unclear if

negative outcomes from infants whose therapies were discontinued were solely related to being taken off cooling or because these infants had some degree of clinical instability during cooling (eg, development of cardiorespiratory instability) prompting discontinuation of the therapy. More studies are also needed in this area to clarify optimal duration of cooling; data to support the practice of early discontinuation of TH are limited.

### Deeper and Longer Cooling

Currently TH recommendations stipulate that infants be cooled at a temperature of 92.3°F to 94.1°F (33.5°C–34.5°C) for an intervention period of 72 hours. (8) However, the idea of deeper (<92.3°F [33.5°C]) and longer (>72 hours) cooling being able to further suppress oxidative metabolism, apoptosis, and inflammation secondary to reperfusion injury has been explored. (9) A 2014 RCT found evidence of deeper cooling at 89.6°F (32°C) being associated with increased use of nitric oxide and extracorporeal membrane oxygenation. In addition, longer cooling is associated with higher risk of arrhythmias and anuria, as well as longer hospitalizations. (9) As such, the study urged practitioners to not stray from the current recommendations for cooling depth and length. (9)

### Neuromonitoring During TH

It is not required that an infant have seizures to qualify for TH. (8) However, seizures are a known morbidity of HIE and factor into the definition of severe encephalopathy. Seizure monitoring is recommended for any infants with concern for ischemic injury, and TH can influence the natural history of seizure activity. (8) Clinicians can monitor for seizure activity in 3 ways: amplitude-integrated EEG (aEEG), conventional EEG, and video EEG (vEEG).

The most commonly used modality for seizure monitoring is aEEG. (17) It is simple to apply to the infant, has been used in large RCTs of greater than 300 infants, and does not require interpretation by a neurophysiologist. However, limitations of this type of monitoring have been uncovered with its concurrent widespread use and acceptance. Interpretation of aEEGs is somewhat user dependent (18); an international survey of neonatologists in 2010 found that many were uncomfortable interpreting the aEEG. (19) Despite this, aEEG is a useful and quick tool that can be used in conjunction with physical examination to prompt the initiation of TH within 6 hours, because it has a 96% sensitivity for predicting seizure activity, but is only 39% specific. (20) It can also predict adverse outcomes in the setting of treatment with TH if the

tracing remains severely abnormal 48 hours into therapy, with a positive predictive value of 85% and diagnostic odds ratio of 67. (20)

Although the use of aEEG is quick and does not need extra subspecialty availability for seizure monitoring, conventional EEG remains the gold standard for seizure diagnosis in infants with HIE. (17) The power of EEG for seizure prediction is further bolstered by the addition of continuous video monitoring of the infant. Use of vEEG provides the clinician with more prognostic power during the course of TH. Normal vEEGs are associated with no or mild brain injury noted on magnetic resonance imaging (MRI) at all time points, and a normal background at the beginning of cooling was predictive of a favorable MRI result. (21) The presence of concerning findings on EEG, such as burst suppression and low voltage patterns, held the greatest prognostic value only after 24 hours of monitoring, with a specificity of 81% at the beginning of cooling that rose to 100% with continued monitoring. (21)

Given that 41% of seizure activity in neonates with HIE is subclinical, (21) neuromonitoring for seizures is needed and encouraged, along with transfer of the neonate to a center that can provide this monitoring. (8) Aside from EEGs, a newer type of neuromonitoring is being explored in HIE: near-infrared spectroscopy (NIRS). NIRS monitoring allows for continuous bedside measurements of regional cerebral mixed venous saturation (rSO<sub>2</sub>) and provides information about oxygen demand and utilization by the brain. (22) Reference values have been identified through study of normal controls and infants with various comorbidities including HIE. Immediately after birth, rSO<sub>2</sub> is between 40% and 56% and increases in the first 2 days, eventually reaching a plateau at 55% to 85% by several weeks of age. (23) Infants with HIE are found to have abnormally high cerebral hyperoxygenation believed to be secondary to low energy metabolism, cerebral hyperperfusion, and impaired autoregulation of cerebral vasculature. (23)

Coupled with other neuromonitoring modalities, NIRS has the potential to offer more prognostic information about the risk of brain injury in infants who are receiving TH. Studies comparing the results of NIRS with EEG and MRI findings of neonates with HIE have small sample sizes, and no large-scale RCTs have supported the routine use of NIRS. (22)(24) In these small studies, infants who were later found to have brain injury despite TH had consistently higher rSO<sub>2</sub> than those who did not, especially within the first 4 days after delivery. (22) Rewarming increased rSO<sub>2</sub>, but again those with brain injury consistently had higher values.

More studies of this modality are needed before it is recommended as a complement to current clinical care.

### Sedation and Neuroimaging After TH

The use of sedation during TH remains highly variable in clinical practice, but is typically used to treat perceived pain and discomfort related to being cold. Postulated benefits include reducing shivering and internal heat generation in addition to alleviating discomfort. One randomized trial specified intermittent morphine or fentanyl for all enrolled infants. (25) However, there are no randomized data comparing groups offered sedation with those without sedation to establish potential impact (positive or negative) on long-term outcomes. There is also concern regarding the impact of hypothermia on drug metabolism. Preclinical experience and existing clinical studies have been reviewed elsewhere. (26)

Neuroimaging is typically performed among infants with HIE, and it is recommended that TH be implemented at centers with MRI capability. (8) Although cranial ultrasonography is the most easily available imaging modality in the NICU, it has very limited ability to reliably identify signs of hypoxic brain injury. (27) Some small investigations have attempted to use dynamic ultrasonography measures such as resistive index to improve diagnostic ability, but data about this modality remain limited. Novel ultrasonography techniques, including the use of contrast agents, may prove useful, but are considered experimental at this time. (28)

MRI remains the mainstay of imaging for detecting hypoxic injury and is recommended for all infants with this suspected diagnosis. The purpose of imaging is 2-fold: 1) to confirm the clinical diagnosis, offer potential insight into the timing of injury, and ensure that another reason for encephalopathy is not incipient; and 2) to provide some insight into the extent of injury and prognosis. Specific sequences that should be obtained include T1/T2 (to differentiate white and gray matter injury) and diffusion-weighted imaging (to assess for cytotoxic edema), at a minimum. MR spectroscopy (to identify lactate and glutamine-glutamate peaks with increased choline and decreased N-acetylaspartate) is also highly reliable for identifying those infants most likely to have neurodevelopmental impairment. Imaging remains an active area of research and novel techniques continue to be developed.

Because of the evolution of injury over time, there is debate about the optimal timing for imaging. Images obtained too early in the course of disease may miss the extent of evolving injury and later imaging may show pseudonormal findings. However, current recommendations suggest that imaging between 7 and 21 days after birth is

appropriate. (8) Some centers pursue early and later imaging, depending on available resources. Finally, very early MRI may be clinically warranted for determining goals of care depending on clinician and family preference.

### SUMMARY

HIE has a complex pathophysiology involving changes in energy utilization of brain parenchyma following a significant peri- or immediate postpartum insult. TH offers neuroprotection to the neonate by dampening cell excitotoxicity and apoptosis, ultimately preserving brain tissue. However, controversy still exists regarding the appropriate use of TH (eg, timing of initiation, duration of therapy, optimal level of hypothermia) and whether utilization can be broadened to additional populations (especially more premature infants). Neuromonitoring during TH in the form of an EEG is recommended for detecting seizures and prognosticating on the severity of HIE. The use of NIRS to monitor cerebral rSO<sub>2</sub> is still under investigation, and no data from large RCTs are available to support its use. Transfer of the neonate with HIE to a center that can provide neuroimaging in the form of an MRI is recommended.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical features, diagnosis, and management of perinatal hypoxic-ischemic encephalopathy.
- Know the causes, clinical features, evaluation, and management of hypoxic-ischemic encephalopathy.
- Know the outcome of infants with hypoxic-ischemic encephalopathy.
- Know the neuroimaging features of hypoxic-ischemic injury in term infants.

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**Caveats of Cooling: Available Evidence and Ongoing Investigations of  
Therapeutic Hypothermia**

Joanna Parga-Belinkie, Elizabeth E. Foglia and John Flibotte

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# Index of Suspicion in the Nursery

## 1 Preterm Neonate with Hydrops and Lactic Acidosis

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### PRESENTATION

A premature female infant is born to a 29-year-old woman with minimal prenatal care at 34 4/7 weeks of gestation, weighing 1,760 g. The woman had been diagnosed with human immunodeficiency virus (HIV) during her second trimester and treated with emtricitabine, tenofovir, and dolutegravir. The infant is delivered via urgent cesarean section because of ultrasound findings of reversed end-diastolic flow on Doppler with category III fetal heart tracings, growth restriction at the 5th percentile, pericardial effusion, and ascites (Fig). Intrapartum zidovudine prophylaxis is administered, but delivery occurred before 3 hours. Apgar scores are 1, 4, 6, and 7 at 1, 5, 10, and 15 minutes, respectively.

Physical examination demonstrates respiratory distress and generalized edema, notably over the extremities and abdominal wall. She undergoes intubation at delivery and initial laboratory tests show thrombocytopenia, elevated transaminases, and significant lactic acidosis (Table 1). Both the mother and infant have type B, Rhesus factor–positive blood.

Platelets are transfused, and nevirapine, lamivudine, zidovudine, and total parenteral nutrition are started. She receives ampicillin and gentamicin for 48 hours, with negative blood cultures. Abdominal ultrasonography on day 1 after birth identifies mild ascites, but no hepatomegaly or liver calcifications. Head ultrasonography finds no evidence of intracranial calcifications.

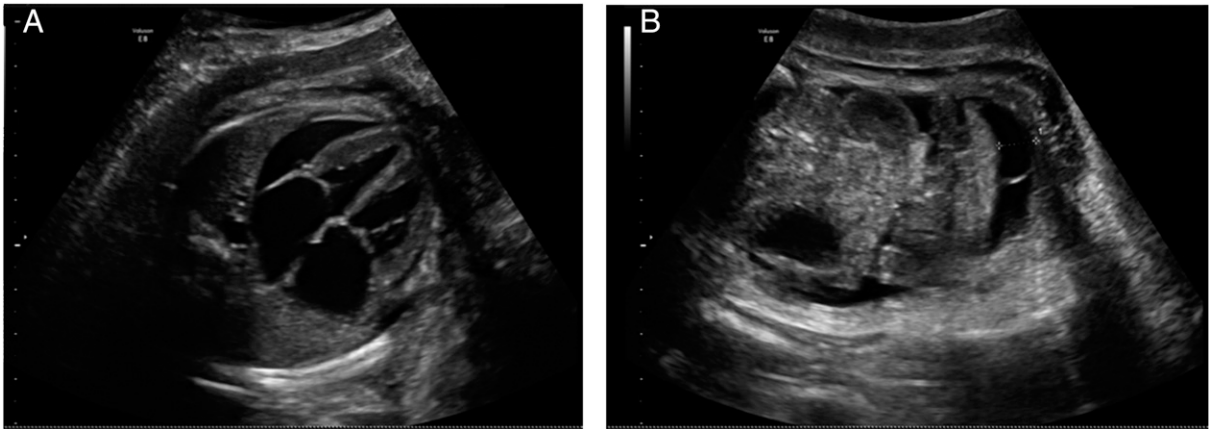
On day 2 after birth, she receives 1 dose of surfactant. Echocardiography is notable for mild right ventricular dysfunction and coronary vasculopathy with mild ectasia of both coronary arteries and a small pericardial effusion. She undergoes extubation 3 days after birth and respiratory support is weaned without further complications.

On day 5 after birth, fresh frozen plasma is transfused for an elevated prothrombin time (26.8 seconds) and international normalized ratio (2.4). Lamivudine and nevirapine are held, given hepatopathy, but zidovudine is continued for the HIV exposure, and ursodiol is started for significant direct hyperbilirubinemia. Ammonia levels are spuriously high (95 µg/dL [68 µmol/L]), likely from delayed laboratory analysis. Iron studies and ferritin are inconsistent with hemochromatosis.

Her generalized edema, liver enzymes, and bilirubin levels improve by the second week of age (Table 2) and ursodiol is discontinued 4 weeks after birth. Total parenteral nutrition is discontinued with advancement of her diet, complicated by hypoglycemia requiring slow weaning of dextrose intravenous fluids. Repeat echocardiography at 3 weeks of age shows improved coronary artery sizes with no evidence of ectasia or aneurysm.

**NOTE** The editors and staff of *NeoReviews* find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in *NeoReviews* when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

**AUTHOR DISCLOSURE** Drs Szafron, Kazerouninia, and Gokulakrishnan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



**Figure.** Pericardial effusion (A) and ascites (B) on fetal ultrasonography.

She is discharged at age 6 weeks and meets developmental milestones at the 2-month follow-up.

#### FURTHER TESTING

Maternal toxoplasmosis, other agents, rubella, cytomegalovirus (CMV), and herpes simplex (TORCH) studies are only positive for CMV viremia, but the patient's urine CMV polymerase chain reaction (PCR) is negative on 2 occasions.

HIV-1 RNA qualitative PCR is negative at birth, 2 weeks, and 6 weeks after birth. Serologies for HSV, parvovirus B19, syphilis, rubella, enterovirus, and toxoplasmosis are negative.

High-resolution cytogenetic analysis and state newborn screening results are normal. Brain MRI shows no abnormalities. She fails an initial hearing screen and auditory brainstem response testing.

Ophthalmologic evaluation at 4 weeks of age shows incomplete retinal vascularization, with no evidence of

**TABLE 1. Initial Serum Laboratories and Arterial Blood Gas Results**

LABORATORY TEST	PATIENT RESULT
White blood cell count	7,200/ $\mu$ L ( $7.2 \times 10^9$ /L)
Hemoglobin	13.4 g/dL (134 g/L)
Hematocrit	40.3%
Platelet	$29 \times 10^3$ / $\mu$ L ( $29 \times 10^9$ /L)
Total protein	3.4 g/dL (34 g/L)
Albumin	2.2 g/dL (22 g/L)
Alanine aminotransferase	298 U/L (4.9 $\mu$ kat/L)
Aspartate aminotransferase	682 U/L (11.4 $\mu$ kat/L)
Alkaline phosphatase	129 U/L (2.1 $\mu$ kat/L)
Total bilirubin	5.4 mg/dL (92.3 $\mu$ mol/L)
Direct bilirubin	0.9 mg/dL (15.4 $\mu$ mol/L)
pH	7.20
Pco <sub>2</sub>	48.4 mm Hg (6.4 kPa)
Po <sub>2</sub>	57 mm Hg (7.6 kPa)
Bicarbonate	18.7 mEq/L (18.7 mmol/L)
Lactic acid	15.65 mmol/L

TABLE 2. Liver Panel, Second Week After Birth

LABORATORY TEST	PATIENT RESULT
Total protein	4.2 g/dL (42 g/L)
Albumin	3.1 g/dL (31 g/L)
Alanine aminotransferase	15 U/L (0.25 $\mu$ kat/L)
Aspartate aminotransferase	28 U/L (0.47 $\mu$ kat/L)
Alkaline phosphatase	219 U/L (3.6 $\mu$ kat/L)
Total bilirubin	1.0 mg/dL (17.1 $\mu$ mol/L)
Direct bilirubin	0.4 mg/dL (6.8 $\mu$ mol/L)

chorioretinitis or neovascularization. After discharge, repeat examination shows normalization of abnormalities.

## DISCUSSION

The differential diagnosis for nonimmune hydrops fetalis (NIHF) includes the following (1):

- Chromosomal abnormalities
- Infectious causes (TORCH infections, parvovirus B19, coxsackievirus)
- Cardiac defects: Structural abnormalities, arrhythmias, high-output heart failure
- Hemolytic and aplastic anemias
- Inborn errors of metabolism
- Placental malformations
- Thoracic, gastrointestinal, or urinary tract defects
- Hepatic disorders such as hepatitis or fibrosis
- Idiopathic

### The Condition

NIHF occurs when there is dysregulation of fluid balance between interstitial and vascular spaces, leading to fluid collection in 2 body cavities or tissue with no history of Rhesus iso-immunization. (1) Classic causes of NIHF were ruled out in our patient. Infectious studies and newborn screening results were normal. Abnormalities related to anatomic defects or infection were not present on abdominal or brain imaging. Our report of an HIV-exposed uninfected neonate elucidates the possible relationship between highly active antiretroviral therapy (HAART) exposure and acute liver injury resulting in NIHF.

Evidence on how in utero HAART exposure affects the neonate is incomplete. However, studies have established the role of nucleoside reverse transcriptase inhibitor (NRTI)-related mitochondrial dysfunction, (2) which can lead to lactic acidosis, a striking laboratory finding in our patient. This is caused by NRTI affinity to mitochondrial

DNA polymerase  $\gamma$  and subsequent alterations in the mitochondrial genome, which encode factors needed for aerobic metabolism. Resulting oxidative stress can lead to lactic acidosis and cell injury affecting many organ systems. (2)

The ascites and pericardial effusions in this patient may have been caused by hepatitis resulting in hypoalbuminemia and right ventricular dysfunction. Her acute liver injury was evidenced by elevated serum transaminases, conjugated hyperbilirubinemia, and impaired hepatic synthetic function with hypoalbuminemia and coagulopathy. Once HAART was halted, the infant showed clinical and serologic improvement. Her marked lactic acidosis makes the HAART regimen a likely culprit. Although cardiac dysfunction is a well-documented cause of NIHF, right ventricular dysfunction was not likely responsible here, given that cardiac function and coronary artery size normalized on repeat echocardiography. Instead, the coronary artery abnormality was likely secondary to increased fetal oxygen demand, and not direct cardiomyocyte damage. In addition, evidence of cardiac consequences caused by in utero HAART exposure is incomplete. (3)

Given the clinical improvement, normal liver ultrasound scan, and reversal of the ascites, hepatitis secondary to in utero exposure to HAART therapy is likely the cause. Although there is no way to prove causality between HAART and NIHF in this patient, our case reveals a potential association between these 2 phenomena and demonstrates the need for further evaluation of this relationship.

### Lessons for the Clinician

- Nonimmune hydrops fetalis is defined as accumulation of fluid in 2 body cavities with no history of Rhesus incompatibility.
- Established etiologies of NIHF include chromosomal abnormalities, cardiac defects, infection, hematologic disorders, gastrointestinal abnormalities, and inborn errors of metabolism.

- HAART exposure in utero can cause lactic acidosis, and may, in an extreme case, result in hepatic dysfunction leading to NIHF.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal HIV infection.
- Know the differential diagnosis and the plan of evaluation and management of a fetus with nonimmune hydrops.

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## Case 1: Preterm Neonate with Hydrops and Lactic Acidosis

Vibha Szafron, Amir Kazerouninia and Ganga Gokulakrishnan

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**Case 1: Preterm Neonate with Hydrops and Lactic Acidosis**  
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# Index of Suspicion in the Nursery

## 2 Severe Respiratory Distress at Birth: A Rare Cause

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### PRESENTATION

A full-term female infant is born with a weight of 2,500 g to a gravida 4, para 2 woman. The mother had no antenatal risk factors and antenatal ultrasound scans are normal. The infant is delivered vaginally and cries immediately after birth. Within a few minutes of birth, she develops severe respiratory distress, and her oxygen saturation drops to 65% in room air. She undergoes intubation in the labor room and is moved to the NICU for mechanical ventilation. Arterial blood gas measurement shows respiratory acidosis, and the ventilator settings are at peak inspiratory pressure of 18 cm H<sub>2</sub>O with a positive end-expiratory pressure of 6 cm H<sub>2</sub>O and FiO<sub>2</sub> of 0.5 with Pco<sub>2</sub> of 68 mm Hg. Chest radiography shows a complete homogeneous opacity in the right hemithorax with dextrocardia (Fig 1).



Figure 1. Chest radiograph showing right-sided homogeneous opacity.

**AUTHOR DISCLOSURE** Drs Kalamdani, Manerkar, Bhisikar, and Mondkar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## PROGRESSION

The infant receives mechanical ventilation for 4 days. Antibiotics are started in view of the homogeneous opacity on the chest radiograph. Septic screening result is negative and blood cultures also turn out negative. Serial chest radiography continues to show the homogeneous opacity in the right hemithorax. Two-dimensional echocardiography is performed in view of the dextrocardia, which reveals dextroposition of a structurally normal heart.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis for a term infant with respiratory distress with persistent right hemithorax opacification includes:

1. Pneumonia—consolidation
2. Collapse of the right lung
3. Bronchopulmonary sequestration
4. Scimitar syndrome
5. Mucus plug in the right main bronchus
6. Pulmonary hypoplasia

## ACTUAL DIAGNOSIS

The opacity in the right hemithorax persists and computed tomography (CT) of the chest is performed. It reveals

complete aplasia of the right lung with absence of right pulmonary artery (Fig 2). Rest of the abdomen and cardiac CT scan is normal. The infant is gradually weaned off mechanical ventilation to high-flow nasal therapy on day 5 after birth. She continues to receive high-flow therapy for 5 more days and then is weaned to room air. Feeds are introduced on day 3 after birth and she starts breastfeeding on day 10. She is discharged from the hospital on day 15 after birth.

## DISCUSSION

Lung agenesis/aplasia is a rare congenital anomaly with most recent estimated incidence of 1.2 per 100,000 live births. (1) It is characterized by the absence of main bronchi, pulmonary vessels, and lung parenchyma. It may be an isolated finding or associated with other anomalies of other organ systems. Commonly associated anomalies include tracheoesophageal fistula, heterotaxy syndromes with cardiac malpositions, aortic stenosis, total/partial anomalous venous connections, and sometimes vertebral defects, *anal* atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VACTERL) anomalies. However, our patient did not have any other congenital anomaly. (2)(3)(4)

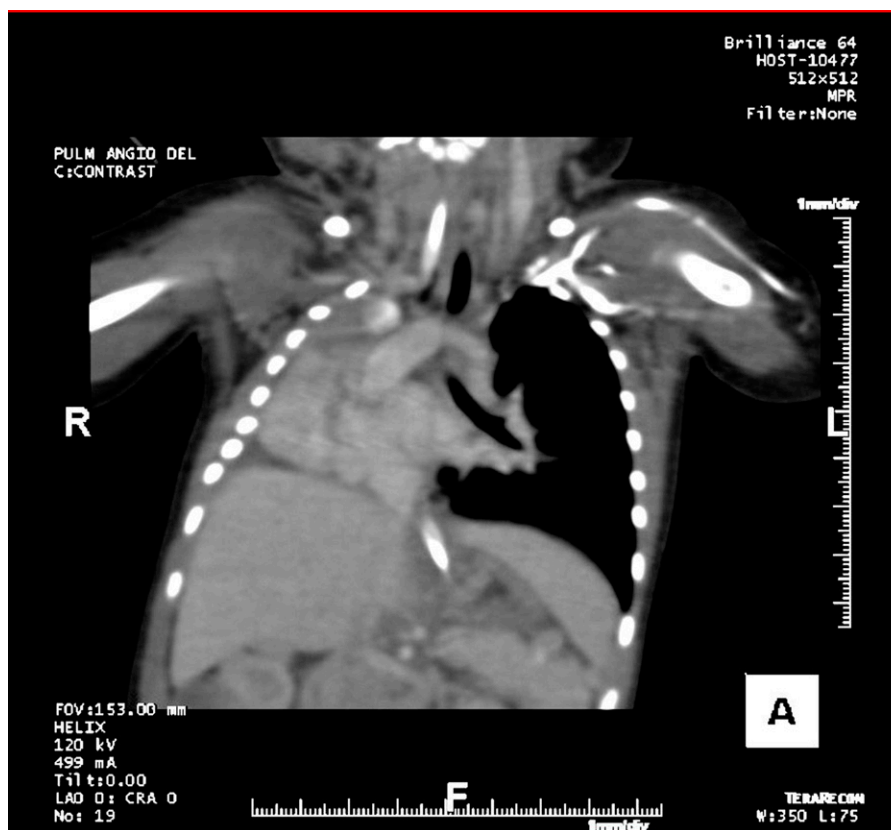


Figure 2. CT scan of the chest showing lung aplasia.

The condition can be diagnosed antenally using ultrasonography and fetal echocardiography. Recently a systematic approach has been developed in assessing lung agenesis, which is associated with cardiac anomalies. (5)

This condition may be asymptomatic at birth and may present in infancy and childhood as a case of respiratory distress or as frequent lower respiratory tract infections. Lung agenesis may present in the neonatal period as a case of respiratory distress or may progress to respiratory failure in severe cases. In our case, respiratory failure was impending in the labor room soon after birth, requiring ventilation. The diagnosis requires a high index of suspicion because the radiographic picture may closely resemble the more common diagnoses of pneumonia/consolidation; the diagnostic modality of choice is CT.

Management in the neonatal period is mostly about respiratory support. It can range from noninvasive respiratory support to invasive ventilation and high-frequency oscillatory ventilation. The degree of respiratory support required and the recovery depends on other associated anomalies and the pathology of the other lung.

The long-term outcomes of patients with lung agenesis are unclear, especially from low- and middle-income countries. The current patient is presently 8 months old without any respiratory morbidity and is developmentally normal.

#### Lessons for the Clinician

- Lung aplasia/agenesis is a rare congenital anomaly and can present with significant respiratory distress at birth or in the first few days after birth.
- Nonresolving pneumonia or a persistent radiographic image of pneumonia/collapsed lung should prompt further investigation for an anatomic abnormality.

- CT is the modality of choice for the diagnosis of this condition.
- With optimum ventilatory support, children with lung aplasia/agenesis recover and lead relatively healthy lives.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the stages and mediators of normal and abnormal cellular and structural development of all components of the lung.

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**Case 2: Severe Respiratory Distress at Birth: A Rare Cause**  
Pavan Kalamdani, Swati Manerkar, Swapnil Bhisikar and Jayashree Mondkar  
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**Case 2: Severe Respiratory Distress at Birth: A Rare Cause**

Pavan Kalamdani, Swati Manerkar, Swapnil Bhisikar and Jayashree Mondkar

*NeoReviews* 2019;20:e524

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# Index of Suspicion in the Nursery

## 3 Late Preterm Infant with Respiratory Distress

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### PRESENTATION

A 2.7-kg male neonate is delivered at 36 weeks' gestation by a 33-year-old gravida 1, para 1 woman via cesarean section. The cesarean delivery was indicated for non-reassuring fetal heart tones and arrest in the first stage of labor. The mother's pregnancy had been complicated by gestational diabetes (managed with metformin), chronic hypertension, and preeclampsia. The family history is not significant for any congenital cardiac defects or genetic syndromes. Fetal echocardiography suggested a coarctation of the aorta at 34 weeks of gestation. Fetal ultrasonography at 28 weeks' and 34 weeks' gestation did not show any anomalies.

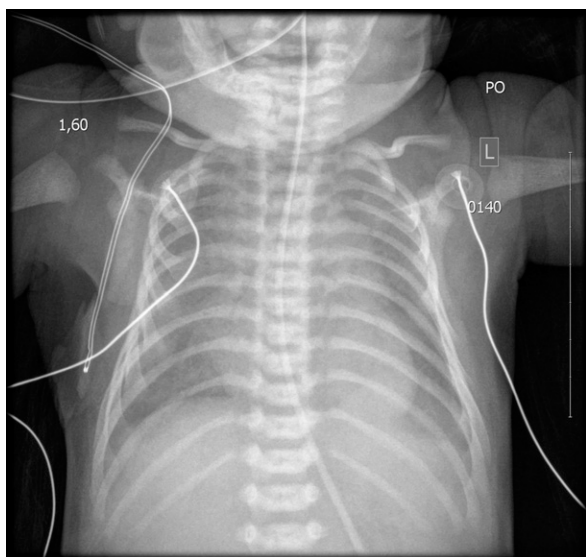
After an uncomplicated delivery (Apgar scores of 8 and 9 at 1 and 5 minutes, respectively), the infant develops mild respiratory distress, which requires continuous positive airway pressure (CPAP). He is admitted to the NICU for anticipatory screening for coarctation and management of his respiratory distress. Chest radiography performed 1 day after birth shows no significant signs of respiratory distress syndrome and normal chest anatomy, with no defects (Fig 1). His respiratory distress subsides within 1 day after birth and feeding is initiated on the same day. Postnatal evaluation, including 4 extremity blood pressure measurements, pre- and postductal saturations, and physical findings, are reassuring within the first 72 hours, though cardiac imaging is yet to be performed. Four days after birth, the neonate develops bilious emesis and respiratory distress, prompting reinitiation of CPAP. Subsequent imaging studies confirm the diagnosis (Fig 2).

### DISCUSSION

Respiratory distress with bilious emesis in the neonate should prompt immediate evaluation and workup. Differential diagnosis in a 3-day-old late preterm neonate includes sepsis, respiratory distress syndrome, malrotation, volvulus, anatomic defects or variants including diaphragmatic hernias, and less commonly, necrotizing enterocolitis. For this neonate's presentation, chest radiography showed concern for loops of bowel in the left chest cavity (Fig 2). With subsequent chest ultrasonography and lateral table tilt chest radiography, the findings were most concerning for a congenital diaphragmatic hernia (CDH) (Fig 3).

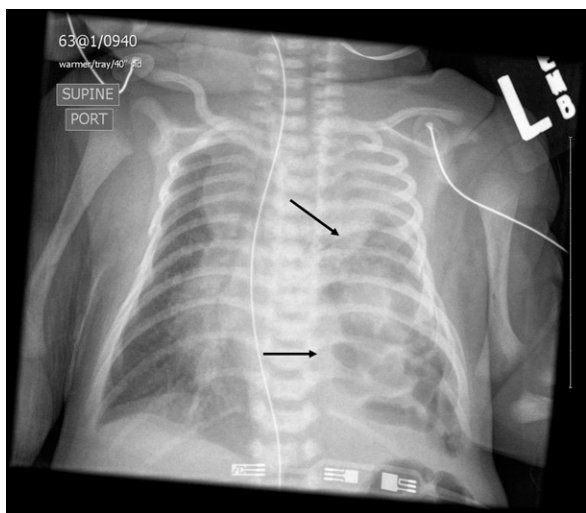
Based on his prior studies and otherwise normal chest radiograph on the first day after birth, late-presenting CDH in the neonate was suspected. We suspected a hernia sac covered most of the defect, and gradual increasing abdominal pressures subsequently displaced portions of the confirmed bowels into the chest cavity.

**AUTHOR DISCLOSURE** Dr Rhine has disclosed that he owns stock in SonarMed, Nfant, and Novonate. Drs Kim and Arain have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

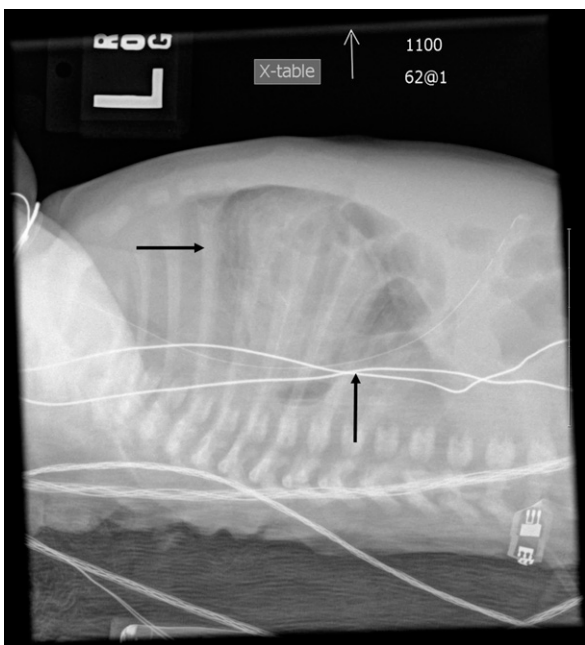


**Figure 1.** Normal anteroposterior chest radiograph first day after birth taken for respiratory distress.

CDH is an opening that forms a communication between the peritoneal and pleural cavities. CDH is one of the most common structural defects occurring in 1 to 4 in 10,000 births. (1)(2) If it occurs in utero, embryologic consequences, including lung hypoplasia and cardiac complications, can lead to poor postnatal outcomes, including death. Speculation on its pathogenesis is thought to be a failure in the embryologic development and closure of pleuroperitoneal folds early in gestation around 4 to 10 weeks. (3)(4)(5) There has not been a clear association with sex, but reports suggest that it occurs in boys more than in girls. (1) Approximately 2.5% to 25% of CDH cases present “late,” which is



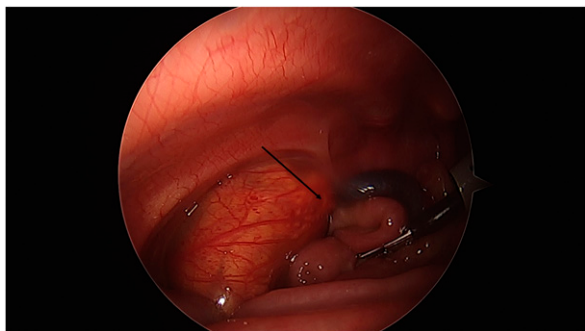
**Figure 2.** Anteroposterior chest radiograph demonstrating loops of bowel in the left pleural space (arrows).



**Figure 3.** Lateral cross-table chest radiograph confirming loops of bowel in the left chest cavity (arrows).

defined as older than 30 days of age at detection. (5)(6)(7) Some retrospective studies speculate that the lower percentage is attributed to the improvement of prenatal screenings and treatment, while rural areas may report higher values because of limited resources. (7) Among these studies, data on the diagnosis of late CDH in the neonatal period are limited and a smaller fraction of the late-presentation groups may be included, because most of these cases may be asymptomatic. (6)(7)

CDH screening occurs at 24 weeks' gestation with prenatal ultrasonography (at least 50% of cases diagnosed), or on rare occasion using fetal magnetic resonance imaging. (8) Postnatal signs and symptoms that should raise suspicion include a scaphoid abdomen in combination with respiratory distress. A CDH can be detected postnatally



**Figure 4.** Thoracoscopic view of the diaphragmatic hernia demonstrating small bowel loops (arrows) in the chest cavity.

with a chest radiograph that displays herniation of abdominal contents into the chest cavity. (8)

A CDH is characterized based on the type of defect and its location. Left-sided hernias are more common, consisting of almost 85% of all reported CDH cases. Locations are labeled as posterolateral (Bochdalek), anterior (Morgagni), or central anterior (septum transversum of the Cantrell type). The defect can also vary within those respective locations and are identified by a letter classification system as described by Ackerman et al. (3) Posterolateral hernias are the most commonly reported type in literature. (4)

Management of CDH is a surgical urgency. Despite the good outcomes of CDH repair with delayed presentation in a neonate, missing the diagnosis could prove fatal. Herniation of the contents with fully developed lungs and vasculature can lead to respiratory distress and cardiac failure. CDH repairs involve thoracoscopic or minimally invasive surgery and the outcomes are usually favorable if detected early. Respiratory support in addition to bowel decompression is suggested to decrease intra-abdominal pressure and to limit the bowel dilation. Enteral nutritional support is withheld before operative repair, because the bowel location in the chest precludes enteral feeds. If prolonged medical resuscitation is anticipated, intravenous access and parenteral nutrition should be initiated.

### Patient Course

The neonate underwent a thoracoscopic diaphragmatic hernia repair. Initial thoracoscopy confirmed a diaphragmatic hernia with the presence of small bowel loops and stomach in the thoracic cavity (Fig 4). Once gently reduced into the abdomen, a type A defect in the diaphragm was identified. In addition, there was a hernia sac encompassing the contents. After mobilization of the hernia sac, the diaphragmatic defect was repaired using interrupted permanent sutures. A pigtail catheter was left for chest drainage and the patient was taken back to the NICU for postoperative care. A repeat chest radiograph was obtained, which showed complete repair of the defect.

The neonate recovered well from the operation and he reached full feeds 12 days after birth and was placed on H<sub>2</sub>-blocker prophylaxis. He was discharged the same day and had no complications.

### Lessons for the Clinician

- Respiratory distress with bilious emesis in the neonate should warrant an evaluation with imaging and the

differential should include anatomic defects such as a late-presenting CDH.

- Although late-presenting CDH may have favorable outcomes, timely management and repair are essential to prevent cardiorespiratory compromise in the patient.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Recognize the imaging features of extrapulmonary causes of respiratory distress.
- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.

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### Case 3: Late Preterm Infant with Respiratory Distress

Michael Kim, Yassar Arain and William Rhine

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## Fetal Decelerations: Use of Vacuum Assistance to Achieve a Vaginal Delivery

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate

**AUTHOR DISCLOSURE** Drs Shear and Young have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles/min, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:
  - Absent: Amplitude range is undetectable
  - Minimal: Amplitude range is greater than undetectable to 5 beats/min
  - Moderate: Amplitude range is 6–25 beats/min
  - Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
  - Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period.
  - Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent.

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes.

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes.
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

#### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:

- Baseline rate: 110 to 160 beats/min
- Baseline FHR variability: Moderate
- Late or variable decelerations: Absent
- Early decelerations: Present or absent
- Accelerations: Present or absent

- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:

- Bradycardia not accompanied by absent variability
- Tachycardia
- Minimal or marked baseline variability
- Absent variability without recurrent decelerations
- Absence of induced accelerations after fetal stimulation
- Recurrent variable decelerations with minimal or moderate variability
- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline

- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:

- Absent variability with any of the following:

- Recurrent late decelerations
- Recurrent variable decelerations
- Bradycardia

- Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## THE CASE

A 31-year-old gravida 1, para 0 woman at 40 weeks and 3 days of gestation with normal prenatal screening results presents in labor. Her prenatal care was unremarkable. Ultrasonography at 38 weeks' gestation revealed an estimated fetal weight of 3,200 g (60th percentile) with normal amniotic fluid. The patient denies pertinent medical, surgical, or family history. She is admitted in labor with a cervical dilation of 4 cm. The FHR tracing is shown in Fig 1.



Figure 1. Electronic fetal monitoring strip 1.



Figure 1. Electronic fetal monitoring strip 1.

Findings in EFM strip 1 are as follows (Fig 1).

- Variability: Moderate.
- Baseline rate: 135 beats/min.
- Episodic patterns: None.
- Periodic patterns: None.
- Uterine contractions: Every 2 to 4 minutes lasting 60 to 100 seconds.

- Interpretation: Category I.
- Differential diagnosis: The fetal tracing is reassuring. There is no evidence of fetal acidosis.
- Action: Expectant management.

The patient progressed spontaneously to the active phase of labor and received regional anesthesia. One hour after epidural placement, a fetal deceleration is noted (Fig 2).

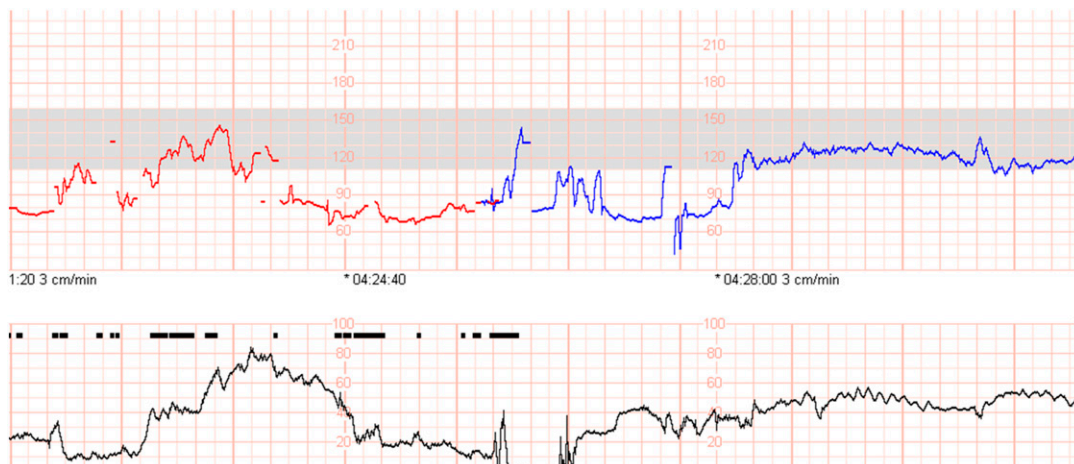


Figure 2. Electronic fetal monitoring strip 2.

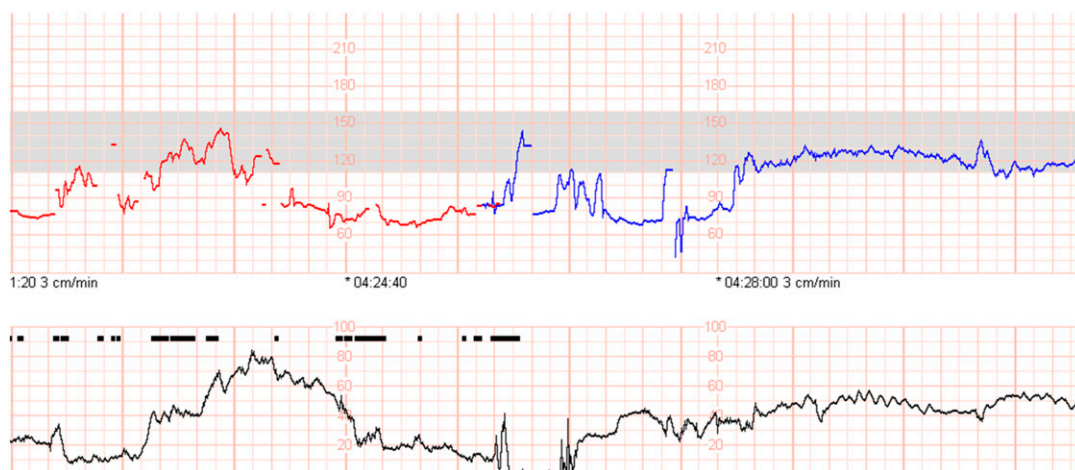


Figure 2. Electronic fetal monitoring strip 2.

Findings in EFM strip 2 are as follows (Fig 2).

- Variability: Moderate.
- Baseline rate: 120 beats/min.
- Episodic patterns: None.
- Periodic patterns: Late deceleration with nadir 70 beats/min.
- Uterine contractions: Every 2 to 8 minutes lasting 60 to 120 seconds.
- Interpretation: Category II.
- Differential diagnoses: Idiopathic placental insufficiency, fetal head compression, umbilical cord compression, placental abruption.

- Action: The patient is repositioned to relieve pressure on the maternal inferior vena cava.

A bolus of intravenous fluid is administered. Abdominal examination reveals no evidence of a tetanic contraction, and cervical examination demonstrates no cord prolapse. The fetal deceleration resolves with these maneuvers. The patient receives expectant management. She progresses to 9 cm dilation with a category I tracing (Fig 3). The maternal heart rate is coincident with the FHR; amniotomy is performed and a fetal scalp electrode is placed to confirm the period of fetal bradycardia. The amniotic fluid is clear.

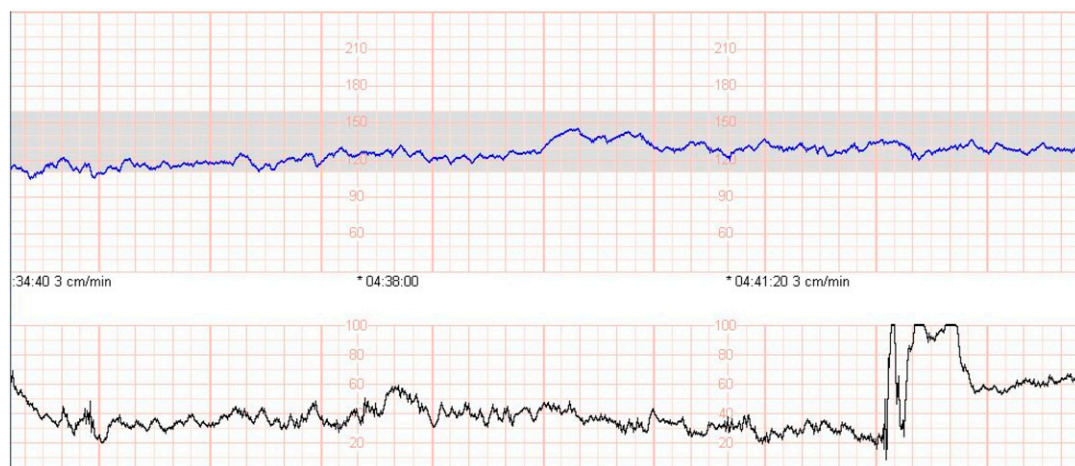


Figure 3. Electronic fetal monitoring strip 3.



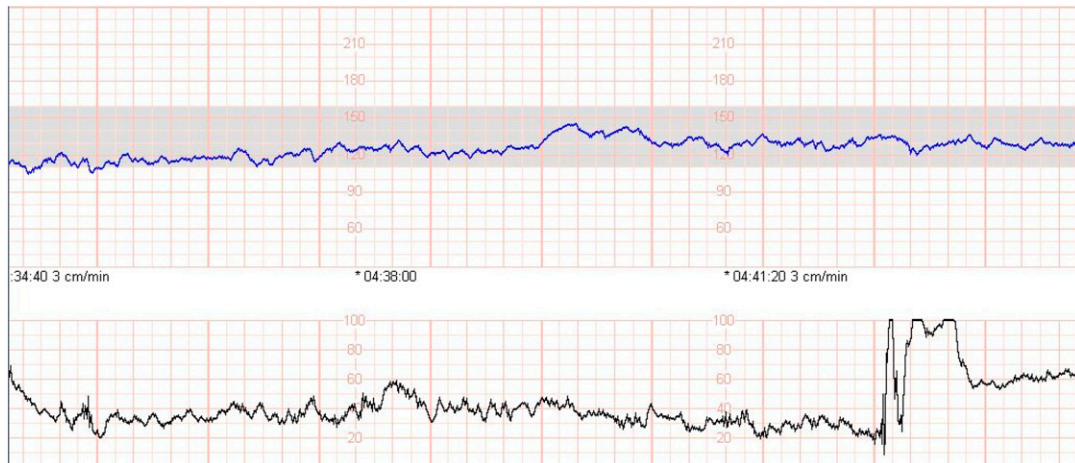


Figure 3. Electronic fetal monitoring strip 3.

Findings in EFM strip 3 are as follows (Fig 3).

- Variability: Moderate.
- Baseline rate: 125 beats/min.
- Episodic patterns: None.
- Periodic patterns: None.
- Uterine contractions: Every 8 to 10 minutes lasting 60 to 100 seconds.

- Interpretation: Category I.
- Differential diagnosis: The FHR tracing is reassuring without evidence of fetal acidosis.
- Action: Expectant management.

The patient progresses to full dilation and begins pushing. Descent of the fetal vertex is noted with valsalva efforts. The FHR tracing is category II, as noted (Fig 4).

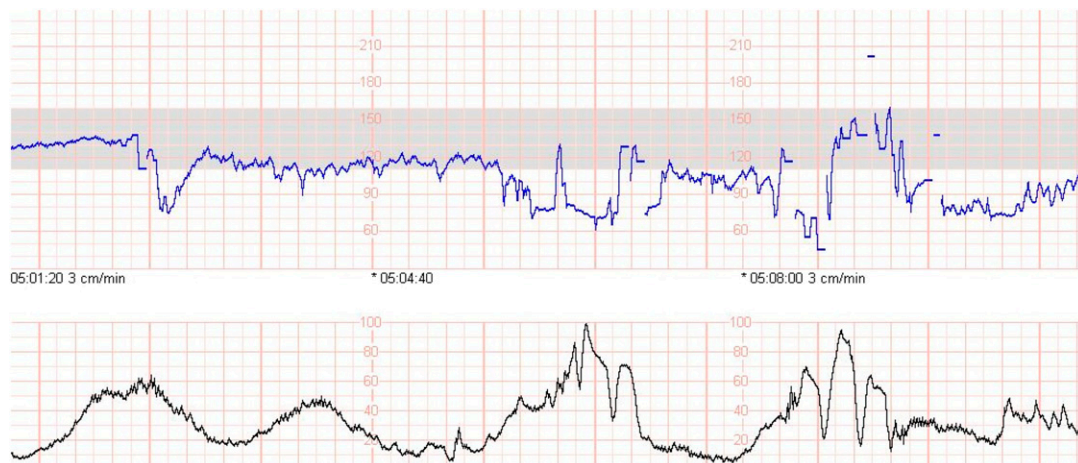


Figure 4. Electronic fetal monitoring strip 4.

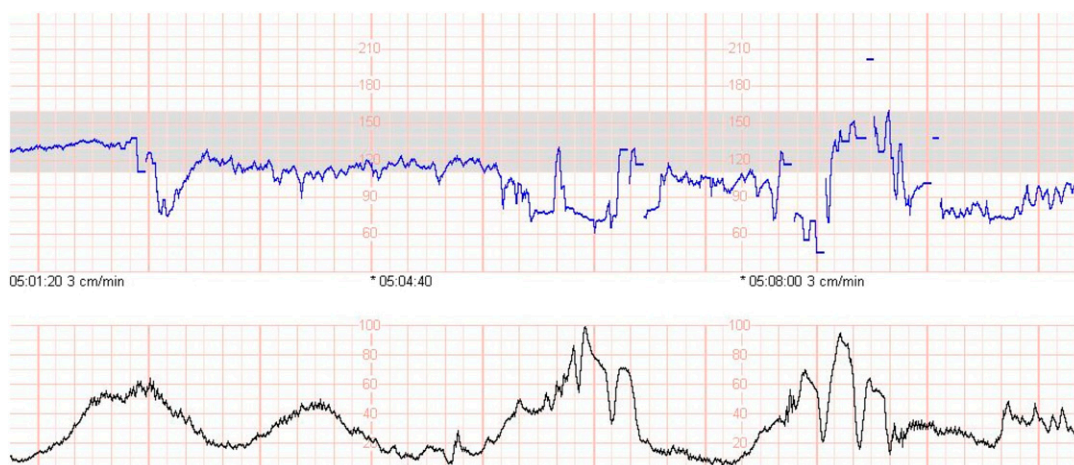


Figure 4. Electronic fetal monitoring strip 4.

Findings in EFM strip 4 are as follows (Fig 4).

- Variability: Moderate.
- Baseline rate: 115 beats/min.
- Episodic patterns: None.
- Periodic patterns: Variable, late, and early decelerations with nadir to 30 beats/min.
- Uterine contractions: Every 90 seconds to 2 minutes lasting 90 to 100 seconds.
- Interpretation: Category II.
- Differential diagnoses: Placental insufficiency, fetal head compression, umbilical cord compression.
- Action: Continue maternal expulsive efforts with consideration of operative assisted vaginal delivery to expedite delivery if the category II tracing persists.

Repeat vaginal examination is performed and the vertex has descended to +3 station. The pelvic outlet is assessed by an obstetrician and found to be adequate. There is no suspicion for macrosomia. The patient reports adequate pain control with the epidural. Her bladder is drained. In the setting of deteriorating fetal monitoring parameters (Fig 5) with prolonged decelerations, options to expedite delivery are reviewed, including vacuum-assisted vaginal delivery or cesarean delivery. The obstetrical team reviews the specific risks of a vacuum-assisted vaginal delivery, including larger degree vaginal laceration, cephalohematoma, scalp laceration, subgaleal hematoma, and rarely, fetal intracranial hemorrhage. The team also reviews the benefits of vacuum-assisted vaginal delivery including expedited delivery and avoidance of abdominal surgery.



Figure 5. Electronic fetal monitoring strip 5.



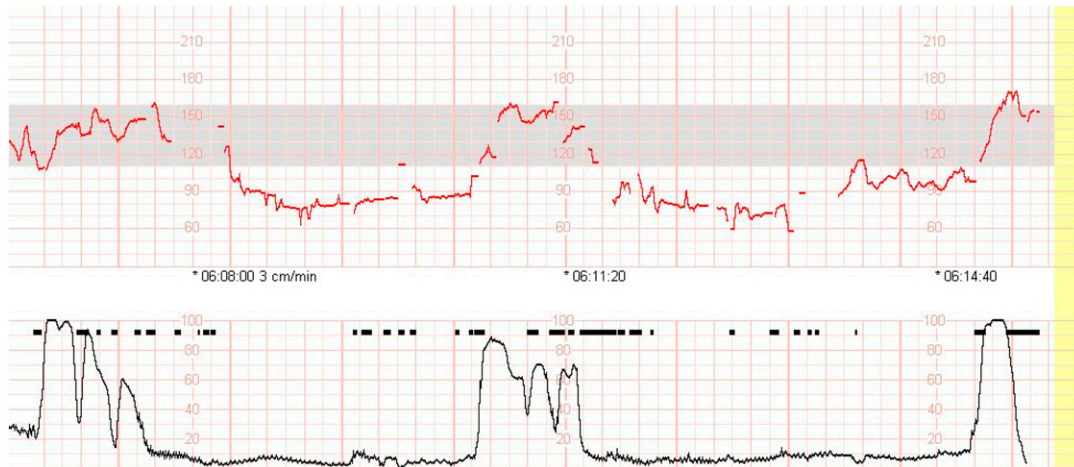


Figure 5. Electronic fetal monitoring strip 5.

Findings in EFM strip 5 are as follows (Fig 5).

- Variability: Moderate with periods of minimal.
- Baseline rate: 135 beats/min.
- Episodic patterns: Prolonged late decelerations with nadir to 59 beats/min.
- Periodic patterns: None.
- Uterine contractions: Every 4 to 5 minutes lasting 90 to 100 seconds.
- Interpretation: Category II.
- Differential diagnosis: Placental insufficiency with deteriorating fetal testing. Recurrent prolonged late decelerations with periods of minimal variability are concerning for fetal acidemia.
- Action: Expedite delivery with vacuum assist.

## OUTCOME

Over the course of 2 contractions, the fetal vertex descends to the perineum with the assistance of the vacuum extractor. On the third contraction, a vigorous male infant is delivered, with Apgar scores of 9 and 9 at 1 and 5 minutes of age, respectively, and a birthweight of 3,350 g. The neonate is placed on the maternal chest. The cord is clamped and cut. Examination of the newborn reveals a right parietal cephalohematoma. The bilirubin level at 24 hours of age is 8.2 mg/dL (140.2  $\mu$ mol/L). The infant is monitored clinically and the cephalohematoma is self-limiting. Two days after birth, the neonate undergoes an uncomplicated circumcision. The infant and mother are discharged in stable condition 2 days after delivery.

## DISCUSSION

Most births in the United States are spontaneous vaginal deliveries without the need for operative assistance. (1) In

the United States, an operative vaginal delivery accounted for 3.3% of all deliveries in 2013. (2) Operative vaginal delivery is used to achieve or expedite delivery. Indications include a prolonged second stage of labor, suspicion of immediate or potential fetal compromise, or shortening of the second stage of labor for maternal benefit. (2) Options for operative delivery include the use of forceps or vacuum assistance. The instrument for operative-assisted vaginal delivery is selected based on provider experience and an assessment of factors that may be contributing to the underlying indication for operative delivery. Prerequisites for operative vaginal delivery include the following (2):

- A cervix that is fully dilated and retracted
- Ruptured membranes
- Engagement of the fetal head
- Pelvis assessed as adequate for vaginal delivery
- Adequate anesthesia
- An empty maternal bladder
- Informed consent
- Willingness of the physician and patient to abandon the attempt if there is failure of the neonate to deliver, which often leads to a cesarean delivery

To perform this procedure, the vacuum cup is placed on the flexion point of the fetal vertex and pumped to the appropriate pressure as indicated by the manufacturer's instructions. The patient is instructed to push with contractions, and downward traction is applied with the vacuum. The obstetrician performing the delivery evaluates for ongoing descent of the fetal vertex. Nursing and physician staff members who are certified in neonatal resuscitation need to be present in the delivery room.

The benefit of vacuum-assisted delivery is avoidance of the morbidities associated with cesarean deliveries, including

bleeding, infection, longer recovery, higher cost, and higher likelihood of future cesarean. At times of impending fetal compromise, operative vaginal delivery can be accomplished faster than cesarean. Vacuum delivery can result in increased maternal and neonatal complications compared with spontaneous vaginal delivery. Maternal risks include a higher likelihood of extensive perineal laceration. Neonatal risks include cephalohematoma (14%) and subgaleal (2.6%) or intracranial (0.1%) hemorrhage. (3) Retinal hemorrhages and increased rates of indirect hyperbilirubinemia have also been reported. The majority of maternal and neonatal patients have no complications.

With appropriate use of an operative-assisted vaginal delivery, a reassuring maternal and neonatal outcome was achieved in this case.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand the rationale, interpretation, and limitations of maternal detection of fetal movement, of the biophysical profile, the non-stress test, and the contraction stress test as means of assessing fetal well-being.

- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor including reassuring and nonreassuring and indeterminate patterns.
- Know how to recognize and differentiate complications of soft tissue injury to an infant's scalp, like caput and subgaleal bleed.
- Know the clinical features and prognosis of birth injuries, such as fractures, lacerations, and facial palsies.
- Know the indications for and perinatal complications of operative vaginal delivery (forceps, vacuum extraction, etc) and of vaginal delivery after cesarean delivery.

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## Strip of the Month: Fetal Decelerations: Use of Vacuum Assistance to Achieve a Vaginal Delivery

Matthew A. Shear and Brett C. Young

*NeoReviews* 2019;20:e530

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## Venous Catheter Tips Need to Stay Out of the Heart

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### CASE 1

A 1,190-g male infant who was one of triplets was born at 27 3/7 weeks' gestation to a 35-year-old gravida 3, para 3 woman. The pregnancy was notable for conception by in vitro fertilization, hospitalization for premature rupture of membranes, and administration of a complete course of antenatal steroids. Because of a prolapsed cord, the triplets were delivered by emergent cesarean section with rupture of membranes 31 hours before birth. The infant had Apgar scores of 6 and 8 at 1 and 5 minutes, respectively. He needed positive pressure ventilation briefly, and was placed on continuous positive airway pressure (CPAP) for mild respiratory distress. Evaluation after birth included a complete blood cell (CBC) count, which was unremarkable, and a blood culture that was negative. The neonatology team placed umbilical arterial and venous catheters. Antibiotic treatment was not started. On day 2, gavage feedings were initiated; on day 3, cranial ultrasonography was performed, the result of which was unremarkable; on day 4, the umbilical arterial catheter was removed; and on day 10, the umbilical venous catheter (UVC) was discontinued.

Over the course of the following 6 weeks, the infant had intermittent abdominal distention with occasional emesis; abdominal radiography was inconclusive for necrotizing enterocolitis (NEC) or bowel obstruction. Because of feeding intolerance, parenteral nutrition was started at 5 weeks via a percutaneous intravascular central catheter (PICC) placed in the right femoral vein. Radiography showed that the tip of the PICC was deep in the right atrium and it remained there. *The plaintiff neonatologist was critical of the catheter not being withdrawn to the junction of the inferior vena cava and the right atrium. The defense maintained that catheters move all the time and it is never really known where they are.* Multiple radiographs were obtained over the next several weeks in an attempt to determine the cause of the abdominal distention and feeding intolerance but were inconclusive; the radiographs consistently showed the PICC tip residing in the right atrium. Many blood cultures and a lumbar puncture were performed to rule out infection, but no infectious origin was determined. Varying combinations of antibiotics were given. The infant continued to have feeding intolerance and abdominal distention.

At 6 weeks of age, the infant was transferred to another medical center for a pediatric surgical evaluation because of persistent feeding intolerance and intermittent abdominal distention. The neonatologist at the referred hospital noted that the distal part of the PICC was coiled in the right atrium and withdrew it 1.5 cm. This repositioning uncoiled the line but the distal tip remained deep in the right atrium. The surgeon thought that the infant's abdominal symptoms were most likely secondary to ileus or to a resultant stricture from a prior silent NEC and recommended a contrast study; this study was unremarkable. Three days

**AUTHOR DISCLOSURE** Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

after admission to the referral center, the infant developed increasing respiratory distress that eventually was followed by cardiac arrest. ***The plaintiff neonatologist pointed out that since the PICC tip was known to be in the right atrium, pericardial effusion and tamponade should have been at the top of the differential. The defense neonatologist disagreed and stated that sepsis was on the top of his list of causes for decompensation.*** The infant's chest and abdominal radiographs obtained during the code showed diffuse haziness in both lung fields, the PICC tip position in the right atrium, and an unremarkable abdomen. The differential diagnosis was septic shock, possibly involving a localized focus, or ischemic/necrotic intestinal organs. Following the prolonged code, a 2-hour period of transient hemodynamic stabilization occurred before the infant suffered a second cardiac arrest for which the decision was made to place the infant on extracorporeal membrane oxygenation (ECMO).

Just after initiation of ECMO, cardiac ultrasonography was performed. It revealed a massive pericardial effusion and showed that the PICC tip was against the anterior portion of the right atrial septum and highly suspicious for perforation. A pericardiocentesis removed 20 mL of milky white fluid that had the same consistency as total parenteral nutrition. The infant developed disseminated intravascular coagulopathy and massive anasarca. Following this, the infant developed multiorgan failure with evidence of extensive central nervous system injury. In the setting of the poor prognosis, the infant was transitioned to comfort care and died. ***The plaintiff neonatologist pointed out that the cardiac tamponade was produced from an erosion of the atrium by the tip of the PICC.*** On postmortem, the infant's right atrial wall had a patchy subendocardial hemorrhage and full-thickness tissue necrosis without evidence of gross perforation. ***The defense neonatologist explained that the mother signed an informed consent and needed to understand that with critically ill infants, adverse events can happen. The plaintiff neonatologist maintained that this was a preventable event if the PICC had been properly positioned. The neonatologist also stated that either a perforation had occurred that had then sealed or that the PICC tip malplacement had led to erosion with endothelial irritation of the atrial wall causing fluids to transmurally cross into the pericardial space.***

## CASE 2

A 2,060-g twin boy was born at 35 3/7 weeks' gestation to a 33-year-old gravida 3, para 2 woman with group B *Streptococcus*-negative status. The pregnancy was complicated by intrauterine growth restriction (IUGR) and pelviectasis. The diamniotic dichorionic twins had 19% discordant growth

discrepancy, with the twin described in this case being larger. A cesarean section was performed secondary to worsening IUGR status. This infant's Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The infant's physical examination findings were normal except for a preauricular tag. After delivery, the infant needed blow-by oxygen and assisted ventilation for 48 hours secondary to retained fetal lung fluid. The infant's CBC count and blood cultures were unremarkable. The team placed a UVC and an umbilical arterial catheter. The tip of the UVC was 2½ cm above the diaphragm in the right heart where it remained without any adjustment. ***The plaintiff neonatologist was critical that the tip was not adjusted to be at the junction of the inferior vena cava and the right heart.*** The infant remained stable, and on day 2, he underwent extubation and feedings were initiated. He rapidly advanced with his nipple feedings and was placed in an open crib. Renal ultrasonography showed mild unilateral hydronephrosis.

On day 4, the nurse noticed that the infant's pulse oximeter was not recording and assumed it was an instrument problem; however, after 30 minutes, she turned the infant supine and noted that he had poor perfusion and was in respiratory distress. ***The plaintiff experts pointed out that the nurse should have evaluated the situation immediately after finding that the pulse oximeter was not registering, to determine if the infant was experiencing a desaturation rather than assume it was an instrument problem.*** The infant's blood pressure was found to be lower than previous readings but was not appreciated as being abnormal. The infant's poor perfusion and respiratory distress persisted for 2 to 3 hours, during which time a CBC, blood culture, electrolytes, and blood gas measurements were obtained and chest radiography was performed. The team started antibiotics and the infant's feedings were held. Three hours after symptoms began, the infant decompensated and required resuscitation with chest compressions and several rounds of intravenous epinephrine. Chest radiography showed hyperinflated lungs, a normal sized heart, and a UVC in the right atrium, curving into the foramen ovale. ***The plaintiff neonatologist pointed out that the team should have first considered a diagnosis of cardiac tamponade as the cause for the infant's decompensation because the UVC was malpositioned. The plaintiff also stated that after the initial insertion and radiographic finding that the UVC tip position was in the heart, the team should have immediately repositioned the line.*** During the code, the infant was placed on prostaglandins and cardiac ultrasonography was performed because of the possibility of a ductal-dependent cardiac lesion. Thirty minutes after the beginning of the code, cardiac ultrasonography was performed, which showed a massive pericardial effusion and the UVC tip was located in the right atrium. Pericardiocentesis was



performed, which resulted in the withdrawal of 15 mL of milky fluid, consistent with parenteral nutrition. The UVC tip was then repositioned to be at the junction of the inferior vena cava and the right atrium. The blood gas after the code showed a pH of 6.8 and a base deficit of 30. *The plaintiff neonatologist pointed out that the infant was feeding well by day 3 and that the UVC was not needed beyond that point. The plaintiff team discussed that a UVC should be removed as soon as it is no longer needed and supplemental fluids should be administered by a peripheral intravenous route. Furthermore, if a UVC is believed to be necessary, the tip needs to be at the junction of the inferior vena cava and the right atrium. The plaintiff neonatologist also noted that there was an argument that the infant might not have even needed the line initially because he was very stable.*

Subsequent to the code, the infant developed seizures, acute renal failure, and hypotonia that subsequently developed into hypertonia. Phenobarbital was started for the seizures. The infant developed noisy breathing that was confirmed to be laryngomalacia. Magnetic resonance imaging showed cerebral cortex infarctions in the parietal and occipital lobes and bilateral intraventricular hemorrhages. The infant's renal ultrasound scan was normal. Over the next weeks, the infant's renal function improved, but the infant developed ex vacuo hydrocephalus. On follow-up examination, he had cerebral palsy, profound developmental delays, and microcephaly. *The defense argued that the preauricular ear tag, pelviectasis, IUGR status, laryngomalacia, hydronephrosis, prematurity, and twin discordancy were indicative of prenatal central nervous system issues that led to the adverse outcome. The plaintiff contended that the misplaced UVC caused the pericardial effusion, the cardiac tamponade, the prolonged code, and the adverse outcome.* The case settled without going to court.

### CASE 3

An 800-g male infant was born at 27 1/7 weeks' gestation to a 28-year-old gravida 5, para 3 woman whose pregnancy was complicated by hemolysis, elevated liver enzyme levels, and low platelets (HELLP) syndrome. After a complete course of antenatal steroids, labor was induced with oxytocin because of worsening blood pressures. Delivery was by emergent cesarean section because of umbilical cord prolapse. The infant's Apgar scores were 3 and 7 at 1 and 5 minutes, respectively. The team placed umbilical lines. The infant received intubation, was given surfactant, underwent extubation later that day, and was then placed on CPAP for mild respiratory distress. The infant's CBC count was unremarkable and the blood culture was negative. He was started on

trophic feedings and total parenteral nutrition was provided through the UVC until day 8, at which point a PICC was placed in the left saphenous vein with the tip located deep in the right atrium. *The plaintiff neonatologist pointed out that the tip should have been at the junction of the inferior vena cava and right atrium. The defense neonatologist claimed that PICCs move all the time.*

On day 2, the nurse contacted the physician 9 minutes after the infant started having desaturations and bradycardia. An emergent radiograph was obtained 22 minutes after the infant's deterioration began, which showed that the PICC tip was in the right pulmonary artery. The infant required a complete resuscitation. *The plaintiff neonatologist stated that a cardiac tamponade should have been highly suspected because the line tip was too high initially based on the radiograph after line placement, and the radiograph during the code suggested even further advancement.* During the prolonged resuscitation, the neonatologist ordered cardiac echocardiography to rule out a ductal-dependent cardiac abnormality. This was performed immediately and showed a massive pericardial effusion with tamponade. Pericardiocentesis was performed and 10 mL of milky fluid was withdrawn. The PICC tip was pulled back to a position at the junction of the inferior vena cava and right heart. Because a spontaneous heart rate could not be achieved, the resuscitation was discontinued after 55 minutes and the infant died. The infant's postmortem examination was unremarkable except for a perforation in the left ventricle. The case was settled without going to trial.

### DISCUSSION

Malposition of central venous catheters can lead to potentially life-threatening complications, including thrombosis, arrhythmia, embolization, portal vein thrombosis, portal hypertension, pericardial effusion, pericardiocentesis, and cardiac tamponade. Clinicians need to be aware of the position of the tip of a central venous catheter and if needed, adjust the line to the correct position. The tip of a PICC placed in the arm or neck should be located at the junction of the superior vena cava and right atrium. The tip of a PICC placed in the leg should end at the junction of the inferior vena cava and right heart. The tip of a UVC should also end at the junction of the inferior vena cava and right atrium, with the exception of a temporary UVC emergently placed after delivery, which requires only a shallow depth until blood return. A good rule for any central venous catheter placement is that the tip should not be within the cardiac silhouette.

An increasing number of centers are using point-of-care real-time ultrasonography to confirm postprocedure catheter tip. One study evaluating the use of ultrasound-guided UVC placement versus standard procedure of advancement to a precalculated distance followed by postprocedure radiography, showed a reduction in procedure time by 64 minutes, and also a decrease in catheter manipulations. Perhaps most importantly, ultrasonography allowed identification of incorrectly positioned catheters in real-time, ensuring immediate removal or adjustment of the catheter and thereby potentially reducing complications. Furthermore, using ultrasonography for serial assessment of catheter tip assessment obviates the need for repeated radiography exposure. In all of the 3 cases presented herein, the catheter tips were positioned unequivocally deep in the cardiac silhouette and did not need ultrasonographic fine tuning.

Why is it important to keep the catheter tip outside the right atrium? The thin layer of endocardium and epicardium of the atrial wall is particularly susceptible to injury or perforation. This tissue has been described as “wet paper” in the newborn because it is extremely vulnerable. The dynamics of fluid moving from the right atrium into the pericardial sac can follow 2 paths. One route that causes a pericardial effusion is direct perforation, with the opening sealing spontaneously after puncture and the catheter potentially adhering to the myocardium, allowing fluid to flow into the pericardial space. The other possibility for the development of pericardial effusion is because of hyperosmolar fluids from the catheter tip causing local endothelial irritation of the atrial wall, thereby leading to transmural transport of the fluids into the pericardial space. Even when small amounts of infused fluid enter the pericardial space, cardiac contractility can be markedly altered in a short period. After a period, a critical amount of fluid in the pericardial sac impedes cardiac contractility, resulting in tamponade. The heart generally will remain normal sized because of acute development of the fluid. Chronic effusion allows the pericardial membrane to stretch without a dramatic hemodynamic impact and the heart size may increase. However, it is very unusual for neonates with a malpositioned PICC or UVC to have chronic pericardial effusions.

When a central catheter is present and the infant has a sudden deterioration, it is imperative that the treating clinicians consider the potential of a malpositioned catheter on top of the differential, evaluate the catheter tip's location, and if found in an incorrect spot, to immediately discontinue the fluids and withdraw the catheter to an appropriate location out of the heart. A malpositioned venous catheter is easy to fix and an adjustment during resuscitation can be

life saving. Infants with a pericardial effusion may present with poor perfusion, weak peripheral pulses, muffled heart sounds, jugular venous distention, and/or decreasing blood pressure. Although pulsus paradoxus and pericardial rub are typically described in infants with a cardiac tamponade, it is very difficult to detect these clinical manifestations in infants.

It is important to remember that even if a catheter was initially placed correctly, the possibility of its migration should always be entertained. In the 3 cases described herein, the initial placement was correct in 1, but the line migrated; in cases 2 and 3, the initial placements were incorrect and were not readjusted until after the infants conditions deteriorated. Echocardiography is the mainstay of diagnosis of a pericardial effusion, but it is not often immediately available in acute circumstances. It is never appropriate to wait for ultrasonography in an infant in acutely deteriorating condition when a venous catheter is involved. Being cognizant of venous catheter positions can help to avoid this scenario. Urgent pericardiocentesis is the primary and only life saving treatment. A videotape of how to perform this procedure can be found at this link: <https://neoreviews.aappublications.org/content/17/10/e627>. Perhaps in the future, clinicians may embark on point-of-care real-time ultrasonography to identify pericardial effusion and cardiac tamponade.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the causes and clinical manifestations of catheter complications of parenteral nutrition.

## Suggested Readings

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#### ANSWER KEY FOR SEPTEMBER 2019 NEOREVIEWS

**Noninvasive Ventilation in the Delivery Room for the Preterm Infant:** 1. B; 2. B; 3. C; 4. C; 5. A  
**Oxygen Therapy for Neonatal Resuscitation in the Delivery Room:** 1. B; 2. A; 3. A; 4. D; 5. A

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## A Newborn with Progressive Generalized Red-Purple Papules and Plaques

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### THE CASE

A term newborn presents with diffuse red-purple papules and plaques on the trunk and extremities immediately after birth (Figs 1–3).

### Prenatal and Birth Histories

- Female infant born to a 21-year-old gravida 4, para 1, white woman
- Pregnancy history: Negative prenatal screening (including rubella immune), positive for gonorrhea (negative test of cure), otherwise uncomplicated pregnancy without any concerns for infection
- Uncomplicated vaginal delivery at 39 weeks, 5 days of gestation at a referring outside hospital
- Apgar scores: 8 and 9 at 1 and 5 minutes, respectively

### Presentation

Immediately after birth, the infant was warmed, dried, stimulated, and placed skin-to-skin on the mother's chest, at which time she was noted to have diffuse papules and plaques on the trunk and extremities (Figs 1–3). She underwent a sepsis evaluation (complete blood cell count/differential, C-reactive protein, blood culture); empiric antibiotics were initiated and she was transported to the regional perinatal center for further evaluation and management.



Figure 1. Back.

**AUTHOR DISCLOSURE** Dr Lee has disclosed that she receives research grants from Eli Lilly, Pfizer, and Regeneron/Sanofi and owns stock in Pyramid Bioscience. Drs Ward, Zimmer, Forcucci, and Southgate have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





Figure 2. Left flank.

### Vital Signs

- Heart rate: 112 beats/min
- Respiratory rate: 43 breaths/min
- Oxygen saturation: 100% in room air
- Blood pressure: 93/64 mm Hg; mean blood pressure: 75 mm Hg
- Temperature: 36.9°C (98.4°F)



Figure 3. Abdomen.

### Physical Examination Findings on Admission 24 hours After Birth

- Growth parameters: Birthweight: 2,980 g (29th percentile); birth head circumference: 32 cm (4th percentile); birth length: 51 cm (79th percentile)
- General: Awake, alert, active, and in no distress
- Head/eyes/ears/nose/throat: Normocephalic, anterior fontanelle open, soft and flat, symmetrical red reflex, ears normal with small preauricular skin tag on the right, nose normal, palate intact
- Cardiovascular: Chest normal, regular rate and rhythm, S1, S2 normal, no murmur, well-perfused, 2+ brachial and femoral pulses equal bilaterally
- Respiratory: Without respiratory distress, breath sounds clear and equal bilaterally
- Abdomen: Normal bowel sounds, soft, nontender, non-distended, no hepatosplenomegaly
- Genitourinary: Normal female genitalia, externally patent anus
- Neurologic: Alert and active, normal tone, normal suck, normal palmar and plantar grasps bilaterally, symmetric Moro reflex
- Skin: Diffuse nonblanching red-purple macules, papules, and plaques scattered over the face, trunk, and extremities (Figs 1–3), negative Darier sign

### Laboratory Studies

- White blood cell count: 14,600/ $\mu$ L ( $14.6 \times 10^9$ /L) with 60% neutrophils, 30% lymphocytes, 8% monocytes, 1% basophils, 1% eosinophils
- Hemoglobin and hematocrit: 19.1 g/dL (191 g/L) and 57%, respectively
- Platelet count:  $156 \times 10^3$ / $\mu$ L ( $156 \times 10^9$ /L)
- C-reactive protein (CRP): <0.6 mg/L (5.7 nmol/L)
- Prothrombin time and international normalized ratio: 11.1 seconds and 1.0 second, respectively
- Partial thromboplastin time: 46 seconds
- D-dimer: 0.483  $\mu$ g/ml
- Uric acid: 2.1 mg/dL (125  $\mu$ mol/L)
- Lactate dehydrogenase: 456 U/L (7.6  $\mu$ kat/L)
- Tryptase: 10.6  $\mu$ g/L (reference  $\leq 10.9$   $\mu$ g/L)
- Aspartate aminotransferase: 35 U/L (0.58  $\mu$ kat/L)
- Alanine aminotransferase: 13 U/L (0.22  $\mu$ kat/L)
- Alkaline phosphatase: 143 U/L (2.4  $\mu$ kat/L)

### PROGRESSION

Throughout the first day after birth, the referring pediatrician noted that the lesions increased in number and became

darker. After the transport team arrived at the referring hospital, the number of lesions appeared to be stable (compared with pictures) with slight fading of the more pronounced lesions. The infant was transferred to a regional perinatal center. After arrival, pediatric dermatology was consulted and a punch biopsy was performed.

## DIAGNOSIS

### Differential Diagnosis

- Congenital leukemia cutis
- Diffuse cutaneous mastocytosis (urticaria pigmentosa)
- Extramedullary hematopoiesis
- Hemangiomatosis
- Histiocytosis
- Multifocal lymphangioendotheliomatosis with thrombocytopenia
- Neonatal fat necrosis

### Actual Diagnosis

Skin biopsy showed a diffuse dermal infiltrate of monotonous cells; immunohistochemical staining with CD117 and tryptase confirmed the diagnosis of diffuse cutaneous mastocytosis (Fig 4).

The infant was discharged from the hospital at 4 days of age, and followed in the outpatient pediatric dermatology clinic. She did well with oral ranitidine treatment and avoidance of triggers of mast cell degranulation. Although the skin lesions did not have a positive Darier sign on presentation, at 2 months of age this characteristic finding of urticaria pigmentosa was present. At 2 months of age, not

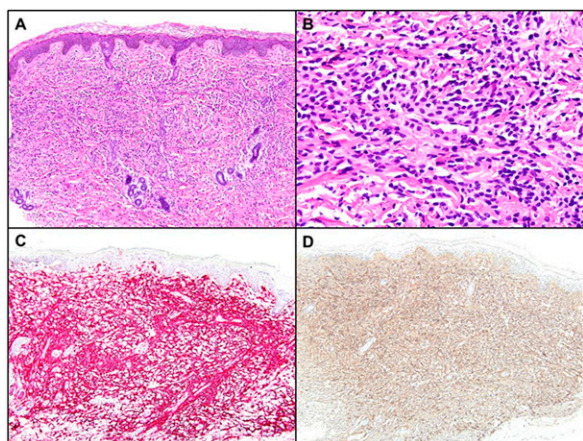
only were the initial cutaneous eruptions still present, but additional lesions had developed (Fig 5).

## WHAT THE EXPERTS SAY

Mastocytosis is a disease of mast cell hyperplasia that can affect the skin, bone marrow, and additional organs such as the liver, spleen, and lymph nodes. It is most common in children but can be seen in adults as well. Both isolated cutaneous lesions (solitary mastocytoma) and diffuse cutaneous eruptions (urticaria pigmentosa), as seen in our patient, can occur. Many patients are minimally symptomatic, but manifestations can include pruritus, flushing, abdominal pain, diarrhea, dizziness, and other systemic symptoms.

Urticaria pigmentosa is the most common type of diffuse mastocytosis. The primary lesion of urticaria pigmentosa, the mastocytoma, is a yellow to brown to red plaque or nodule on the skin. Stroking a lesion often leads to urtication (Darier sign), which is seen in most individuals; in younger individuals, blistering may occur after urtication. Although rare, cases of congenital urticaria pigmentosa have been reported, (1)(2)(3)(4)(5)(6) Ben-Amitai et al (1) report that nearly 20% of pediatric patients with urticaria pigmentosa are initially seen at birth. In most children with urticaria pigmentosa, the disease does not resolve before adolescence. (7)

The diagnostic evaluation of urticaria pigmentosa in neonates begins with a history and physical examination (including constitutional symptoms as well as examination of lymph nodes, liver, and spleen), complete blood cell count with manual differential, serum tryptase, and liver function tests. (8) Improvement in a patient's symptoms correlates with the tryptase level, which is a reflection of mast cell degranulation. Isolated elevation in the serum tryptase by



**Figure 4.** Dermatopathology. A diffuse dermal infiltrate of monotonous cells is seen in panel A (H&E, 40×) and panel B (H&E, 400×). The immunohistochemical stains CD117 in panel C (red chromagen, 40×) and tryptase in panel D (brown chromagen, 40×) confirm the infiltrate is composed of mast cells.



**Figure 5.** Frontal view at 3 months of age.

itself does not necessitate bone marrow biopsy; however, organomegaly, which is more indicative of systemic disease may signify the need for bone marrow biopsy. (9) Because extramedullary hematopoiesis is in the differential diagnosis, a detailed history for toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex (TORCH) infections, as well as pertinent laboratory studies should also be considered in congenital cases.

For patients with urticaria pigmentosa, the management is primarily symptomatic, with an emphasis on avoidance of triggers of mast cell degranulation. Triggers that can precipitate symptoms of mastocytosis include change in temperature, spicy foods, exercise, alcohol, and medications such as aspirin and other nonsteroidal anti-inflammatory drugs, polymyxin B, anticholinergic medications, and certain systemic anesthetics. Patients with mastocytosis may have delayed anaphylaxis after general anesthesia, so overnight postoperative monitoring is recommended. (10) Local treatment may consist of topical or intralesional corticosteroids and topical calcineurin inhibitors, while systemic treatments include oral antihistamines and oral cromolyn sodium (especially for gastrointestinal symptoms). Systemic treatment for more severe cases includes other targeted agents. (8)(11)(12) Of note, the local and systemic treatments are not approved by the Food and Drug Administration and are off-label use. Finally, some individuals with severe mastocytosis are at risk for systemic hypotension and should be treated with injectable epinephrine. (8)(11)(12)

This case highlights the diagnostic capability of a skin biopsy in narrowing the differential diagnosis of skin lesions. In our patient, biopsy was able to rule out congenital leukemia cutis (absence of infiltrative leukemic cells), extramedullary hematopoiesis (absence of erythrocytes, leukocytes, and megakaryocytes), hemangiomas (absence of small vessel proliferation), histiocytosis (absence of Langerhans cells), multifocal lymphangioendotheliomatosis (absence of small vessel proliferation, lined with endothelial cells and thrombocytopenia), and neonatal fat necrosis (absence of fat necrosis and needle-shaped clefts within the fat cells).

## SUMMARY

- Although newborn rashes are very common, any newborn with diffuse nonblanching red to brown papules and plaques requires prompt evaluation.
- The initial workup of these eruptions in newborns should include infectious (TORCH) and malignant etiologies.

- Dermatology should be consulted as soon as possible for evaluation and consideration of biopsy.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the cutaneous manifestations of neonatal hematologic disorders such as thrombocytopenia and coagulation disorders.

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**A Newborn with Progressive Generalized Red-Purple Papules and Plaques**  
Price S. Ward, Katelyn Anderson Zimmer, Jessica A. Forcucci, Lara Wine Lee and  
W. Michael Southgate  
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# Historical Perspectives

## Low Birthweight and Preterm Infants in Indonesia

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### Abstract

The incidence of infants with low birthweight (LBW), prematurity, and small for gestational age (SGA) in Indonesia remains high, and the morbidity and mortality in these infants are significant. To study these groups of infants in Indonesia, the author searched PubMed/Medline, the Cochrane Library, Google, Indonesian reports, local publications, and doctoral and master theses in English and Indonesian from 1987 to February 2019. In this review, the development of local reference growth charts of infants born in Indonesia is described, as well as the importance of these curves in defining the prevalence of SGA infants. Some of the risk factors associated with LBW, preterm, and SGA Indonesian infants are described. The author also discusses the effectiveness of specific interventions, such as kangaroo mother care, early initiation of enteral feedings, increased breastfeeding rates, and identifying the optimal timing of hospital discharge. Some of the morbidities associated with LBW infants born in Indonesia are described. Advances in hospital care and postdischarge follow-up of LBW, preterm, and SGA infants born in Indonesia are critical to decrease the morbidity and mortality rates associated with these populations.

### Objectives After reading this article, the readers should be able to:

1. Thoroughly comprehend the risk factors, care interventions, neonatal morbidity and mortality of low birthweight, preterm, and small for gestational age infants in Indonesia.

### INTRODUCTION

In Indonesia, the incidence of infants born with low birthweight (LBW), prematurity, and small for gestational age (SGA) is high, and the morbidity and mortality in these infants is significant. These terms are used globally and are defined as:

- LBW: Infants with birthweight less than 2,500 g
- Prematurity: Infants with birth gestational age less than 37 weeks or less than 259 days

**AUTHOR DISCLOSURE** Dr Haksari has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

AGA	appropriate for gestational age
CPAP	continuous positive airway pressure
IVH	intraventricular hemorrhage
KMC	kangaroo mother care
LBW	low birthweight
NEC	necrotizing enterocolitis
PDA	patent ductus arteriosus
ROP	retinopathy of prematurity
SGA	small for gestational age
SUMMIT	Supplementation with Multiple Micronutrient Intervention Trial
VLBW	very low birthweight

- SGA: Infants with birthweight less than the 10th percentile for gestational age

LBW is associated with both prematurity and SGA. (1) The high population of SGA infants in low- and middle-income countries is a significant health care burden.

To examine these high-risk groups of infants in Indonesia, the author searched PubMed/Medline, the Cochrane Library, and Google for relevant studies about LBW, preterm, and SGA infants published from January 1, 1987, to February 15, 2019. She also searched Indonesian reports, local publications in English and Indonesian, and doctoral and master theses pertinent to this topic. In this review, the development of local reference birthweight charts of infants born in Indonesia is described as well as the importance of these curves in defining the prevalence of SGA infants. The risk factors associated with LBW, preterm, and SGA infants are highlighted. Specific interventions are discussed, such as kangaroo mother care, early initiation of feedings, increasing rates of breastfeeding, and identifying the optimal timing of hospital discharge, which could minimize the morbidity and mortality in these populations. The author concludes by describing some of the morbidities associated with LBW infants born in Indonesia. This review highlights the importance of advancing care both in the hospital and after discharge of LBW, preterm, and SGA infants born in Indonesia to decrease the morbidities and lower the mortality associated with these populations.

## BIRTHWEIGHT MEASUREMENTS IN INDONESIA

Early identification of LBW cases is required to reduce infant morbidity and mortality. In Indonesia, 89.4% of newborns are weighed at birth. (2) In some provinces in the eastern part of the country, most deliveries take place at home and are assisted by traditional birth attendants. In most of these cases, the newborn's birthweight is not recorded because of lack of weighing scales and/or lack of skills of the health personnel in performing the measurement, especially in rural areas. To assess whether anthropometric measurements such as calf, chest, and head circumference were reliable substitutes for identifying LBW infants, a cross-sectional study was conducted in Banjar Baru, South Kalimantan. (3) This study found that calf circumference was the most suitable measurement for a substitute of birthweight, if birthweight was not obtained. (3)

## DEVELOPMENT OF LOCAL BIRTHWEIGHT REFERENCE CURVE IN INDONESIA

The prevalence of SGA infants depends on the reference birthweight curve that is used. When the curve is based on

the local data of infants from a low-to middle-income country, the prevalence of SGA decreases. Therefore, updated regional birth curves are more applicable to classify SGA infants and to identify newborns requiring attention. (4)

Haksari et al established updated local birthweight, length, and head circumference curves of infants in Indonesia. (5) Birthweight curves were constructed based on 54,599 eligible newborns with mean  $\pm$  standard deviation measurements that were divided into 3, 5, 10, 25, 50, 75, 90, 95, and 97 percentiles in the table and graph. (5) Gestational ages were determined by the Dubowitz gestational age assessment score, and if possible, confirmed by the date of the mother's last menstrual period. The birthweight curves that were developed were unique as they focused solely on infants from Indonesia with a birth gestational age as low as 26 weeks' gestation. (5) The birthweight curves showed that male infants born at term had a significantly higher mean birthweight than did female term infants, and first-born term infants had lower weights at birth than did later-born children. (5) These differences, however, were not found in infants born preterm.

## SGA INFANTS

Some studies have evaluated the outcomes of SGA infants born in Indonesia. One study found that hearing loss was more common in SGA infants compared with appropriate-for-gestational age (AGA) infants. (6) The mean aortic wall intima-media thickness has been found to be significantly higher in SGA than in AGA newborns. (7) The mortality prediction score for SGA infants is a simple scoring system that predicts the mortality of SGA infants based on gestational age, birthweight, Apgar score at 1 minute, any period of hypothermia, and a diagnosis of pneumonia. (8) Predictors of mortality for symmetrical SGA infants were investigated and include birthweight less than 1,500 g, Apgar score less than 4 at 5 minutes of age, presence of a congenital anomaly, and a diagnosis of necrotizing enterocolitis (NEC). (9)

Trends in growth velocity in infants from Indonesia have also been examined. Data have shown that very-low-birthweight (VLBW, <1,500 g) infants who were also SGA had lower growth velocity than infants who were AGA. (10) Importantly, preterm infants born between 28 and 32 weeks' gestation required the longest time to regain birthweight but had the greatest growth velocity. (6) SGA infants with catch-up growth at 2 to 3 years of age were found to have significantly better gross motor, fine motor, and problem-solving performance than those without catch-up growth. (11)

## RISK FACTORS OF PRETERM BIRTH IN INDONESIA

In 2010, Indonesia ranked fifth in the world for the number of premature births, with a preterm birth rate of 15 per 100 live births. (2) The causes of preterm birth are complex and multifactorial. The significant risk factors associated with preterm birth in Indonesia include limited antenatal care, (12)(13)(14) young maternal age, (12)(14) history of prior preterm birth, maternal diseases such as anemia and hypertension, antepartum hemorrhage, (14) leukorrhea, and premature rupture of membranes. (13) Risk factors associated with LBW in Indonesia were low level of maternal education, poor maternal weight gain during pregnancy, short interval between pregnancies, previous history of LBW delivery, and maternal illness during pregnancy. (15)

The Supplementation with Multiple Micronutrient Intervention Trial (SUMMIT) examined the determinants of LBW, SGA, and preterm birth in infants from Lombok, an Indonesian island. (16) Data from this double-blinded, cluster-randomized, controlled trial were analyzed and showed that approximately 33%, 13%, and 13% of the determinants of LBW, SGA and preterm birth, respectively, were preventable. (16) Improved maternal education, better nutrition, increased household wealth, and use of family planning measures were key determinants of improved birth outcomes. (16)

In a cohort of 11,101 infants from the SUMMIT group who were weighed within 1 hour of birth, infants born to women who received multiple micronutrients had a 14% lower risk of LBW than infants born to women who received iron and folic acid alone. (17) Multivitamins provided to pregnant women were as effective as iron/folic acid at improving the anemic status of women, and appeared to have other benefits for maternal and child nutritional status. (18) Thus, maternal multiple micronutrient supplementation should be an important component for enhancing prenatal care programs. (17)

A secondary analysis of data collected between 1993 and 2007 by the Indonesia Family Life Survey, the first national prospective longitudinal cohort study in Indonesia, found that maternal, but not paternal, smoking was associated with a significant reduction in birthweight, a lower birth gestational age, and an increased risk of preterm birth. (19) However, in urban areas, infants born to fathers who smoked and smoking parents (>20 cigarettes/day for both cases) had significantly lower birthweight. (19)

A case-control study conducted in Banjar, a malaria endemic area of South Kalimantan, studied 130 women divided into 2 groups, 65 women who delivered LBW infants (case group) and 65 women who delivered infants with

appropriate birthweight (control group). (20) Multivariate analyses revealed that determinants of LBW were antenatal care, advanced (>35 years old) and young (<20 years old) maternal age, and anemia. The study recommended that pregnant women at high risk of delivering an LBW infant should receive routine antenatal care. (20)

Bacterial vaginosis, diagnosed early in the second trimester of pregnancy, is also a significant risk factor for preterm delivery in Indonesia. (21) In addition, the preterm birth rate increased during the 1997 economic crisis in Indonesia based on a comparison study of live births between October 1996 and December 1998 at Hasan Sadikin Hospital (Bandung, Indonesia), (22) likely related to nutritional factors.

## IMPROVING NEONATAL OUTCOMES IN INDONESIA

### Kangaroo Mother Care in Indonesia

Kangaroo mother care (KMC) was first introduced to Indonesia in the 1990s as a new, cheaper, and simple method of caring for LBW and preterm infants, replacing incubator or crib care. (23) In this approach, mothers place their infants skin to skin and frequent breastfeeding is encouraged; this occurs while infants are hospitalized and continues after discharge. At Sardjito General Hospital (Yogyakarta, Indonesia) KMC was first implemented in 1995 as part of a multicenter research project. It was also presented for the first time at the National Child Health Congress X in Bukittinggi in 1996 and at the Indonesia Perinatology Congress (Perinasia) VI in the same year in Manado. In 1999, it was applied at the Mataram Hospital in West Nusa Tenggara. (23)

**Benefits of KMC.** KMC has proven to be effective in Indonesian hospitals, (24)(25) and has been shown to decrease the incidence of hypothermia in LBW infants. (26)(27)(28)(29) In addition, KMC has been shown to stabilize the physiologic parameters of LBW infants if used in the first 4 hours after birth. (30) The lateral decubitus position, as opposed to the prone position, may significantly reduce infant crying. (31) A combination of KMC and lullaby music has been shown to be effective for maintaining normal vital signs such as temperature, respiration, and oxygen saturation in hospitalized infants in Indonesia. (32)

In Indonesia, use of KMC has also been shown to significantly improve infant weight gain. (33)(34)(35)(36) It has been suggested that KMC also improves weight, supine length, and head circumference for age, though these increases were not found to be statistically significant. (37)(38) In addition, KMC has positive effects on breastfeeding (26) (T Tunggal, M Hakimi, EL Haksari, unpublished

observations) and breast milk production. (27) Although one study was unable to achieve exclusive breastfeeding rates, (29) a study by Cattaneo et al (24) and a report from Sardjito Hospital demonstrated that KMC was associated with exclusive breastfeeding in 88% and 98% of mothers, respectively. (Sardjito Hospital, unpublished report, 2016) In addition, 1 month after hospital discharge, infants who had received KMC during their hospitalization were still being exclusively breastfed. (25)

**Mother and Staff Acceptance of KMC.** KMC has generally been well accepted by mothers (24)(25)(39) and hospital staff. (23)(25)(40) However, qualitative studies, in-depth interviews, and group discussions indicate that hospital staff needs to intensively promote KMC for it to be successful. Maternal knowledge and positive attitudes about KMC help improve its practice. (41) A study at one district hospital in a big Indonesian city found that mothers were more likely to practice KMC if hospital staff promoted the practice and provided education. (42)

Mothers who use KMC also benefit. (39) Studies have shown that KMC reduced postpartum depression. (29)(43)(44) One study that was conducted at 3 hospitals in Yogyakarta found that the depression score in the KMC intervention group was 3 times lower than the group without KMC intervention after adjusting for parity (95% confidence interval, 1.92–4.3). (43)

**Implementation of KMC in Hospitals.** The introduction of KMC at a hospital requires the support of hospital management, detailed policies for using KMC, a description of the standard operating procedure of KMC, educational brochures for families, and information for medical staff. (45)(46) KMC brochures for mothers and staff need to be revised regularly. KMC is included in the medical record of LBW infants at level 3 or level 2 hospitals. After LBW infants are discharged, their parents should continue to monitor their infant's temperature, feeding, stool and urine output, and KMC periods.

Hospitals can decide to use 1 of 2 kinds of KMC: continuous or intermittent KMC. Continuous KMC refers to the attachment of an LBW infant to the mother for almost 24 hours per day while intermittent KMC refers to an attachment that lasts for several hours per day. Some Indonesian hospitals implement continuous KMC, while others apply intermittent KMC. (39) Special rooms for KMC in the neonatal ward are often equipped with rocking chairs. Other hospitals, however, only have small rooms or mattresses. (46)

For twins with LBW, KMC can be performed by the mother and father or another relative. (46) If the mother is very ill or does not survive, the infant's father or relative can be the primary provider of KMC.

For the KMC program to be successful, a conducive environment with adequate facilities and holders (ie, supports for the infant) is required. Capable and experienced trainers, and support from the mother's family and the director/head of the hospital/health center are also needed.

Security for infants in the ward includes closed circuit television, 24-hour security staff, and identity bracelets for the newborn (blue for boy, pink for girl) and mother (pink for the inpatient mother and white for outpatient mother). The father or relative wears a white bracelet when practicing KMC. (Sardjito Hospital, unpublished report, 2016) Hospital policy and standard operating procedure for KMC have to be continuously enforced because KMC is one of the factors that are evaluated when hospitals are accredited. (47)

Bergh et al (23) reported that hospital implementation of KMC was a long process that required dedication and support for several years. The authors determined success of implementation based on achievement of 6 stages:

- Creating awareness about KMC
- Adopting the practice of KMC
- Taking ownership
- Showing evidence that KMC is occurring
- Regularly integrating KMC into practice
- Sustaining KMC in practice

A study on KMC implementation at 10 hospitals showed good acceptance of the practice with only 1 hospital that was unable to show that KMC was occurring. (16) Of the remaining hospitals, 5 showed that KMC was occurring and 4 were able to integrate KMC into their practice, 2 of which almost achieved evidence of sustaining KMC. (16) In practice, the implementation of KMC at hospitals is usually initiated by pediatricians who work in the neonatology division. (48) Continued use of KMC and dissemination of KMC to other local hospitals requires support and motivation by regional pediatricians as well as demonstration of benefits to the participating infants and mothers. (46)(49)(50)

**Staff KMC Training.** KMC training material for staff includes practical guidelines, flipcharts, and videotapes. The government conducts staff training at some facilities. (51) Since 1997, Perinasia has held KMC training. Some centers and professional organizations hold KMC training as well. (48)(52) Instruction in KMC is also included in training on transportation of LBW infants and during neonatal resuscitation training by the Indonesian Pediatric Society.

In Indonesia, the primary health care services are conducted at health centers. District hospitals are secondary health facilities that provide referral services in the area. Tertiary health facilities are available at teaching hospitals,



which are usually located in the provincial capital. In provinces without teaching hospitals, however, the services are provided by the provincial government hospital in the capital of the province. (5)

Thus far, KMC training has been coordinated with the health office of the Indonesian government, is directed toward high-risk neonates (eg, diagnosis of LBW, asphyxia, sepsis, feeding difficulties), and is held once or twice a year. The government's health office personnel and a neonatologist visit the health centers and district hospitals 6 months after the implementation of KMC to evaluate, provide refresher courses, and provide feedback about management for high-risk neonates. KMC and LBW care information is also disseminated to other health offices and hospitals. (45)

**Initiation of KMC.** KMC should ideally be initiated as early as possible through skin-to-skin contact once an infant achieves cardiorespiratory stability. (53) Sardjito Hospital and some other hospitals initiated KMC practice in stable infants, including infants receiving continuous positive airway pressure (CPAP), but not those who were intubated, regardless of gestational age. Even though some hospitals initiate KMC soon after birth, Pratiwi et al found that infant age greater than 10 days was a prognostic factor for KMC success in LBW infants. In this study, the authors define success of KMC as the ability to achieve weight gain and stabilization of the infant's heart rate, temperature, and respiratory rate. (54)

After the decision is made to introduce KMC, the nurse helps the mother hold the infant. (45) Each hospital has a specific holder (carrying pouch, "Thari" holder, or traditional holder) that the mother can use to stabilize her infant; maternal comfort scores have been similar for all holders. (55) Staff members also teach the mother about breastfeeding, how to label expressed breast milk, and properly store and transport their expressed milk.

In Indonesia, KMC is commonly initiated in health facilities, especially at hospitals. Sometimes, it is conducted at clinics or health centers. KMC practice can be continued in the community and at home.

**Challenges and Obstacles in KMC Practice.** Despite the benefits that KMC offers in the care of premature and LBW infants, this relatively new health care intervention is complicated. The implementation of KMC into hospital practice creates many challenges. For example, some health care personnel do not have adequate knowledge about or experience with KMC, some neonatal staff lack confidence in instituting KMC in the care of LBW infants, and some hospitals lack support from the hospital board of directors.

Improvement of KMC practice requires well-organized plans, support from the government and related professionals

(pediatricians, midwives, nurses, psychologists, and members from the public/community health sciences with a specific interest in KMC), and budget planning. (48)(56) KMC in Indonesia has been practiced sustainably at some hospitals and efforts have been made to improve the success of KMC. Some hospitals initiate KMC for research purposes or for hospital accreditation.

### Optimal Timing of Discharge from the Hospital

The timing discharge of LBW infants at some Indonesian hospitals is based on the Davanzo criteria, which include (57):

- Stable clinical condition
- Sufficient sucking and swallowing
- Normal body temperature for 3 days without need for equipment support
- Birthweight regained and weight at discharge greater than or equal to 1,500 g
- Demonstrated weight gain for 3 days
- The mother's ability to care for her infant

There is no requirement to attain a specific gestational age at the time of discharge if the aforementioned criteria are met.

Other hospitals, however, use the Perinasia score, which is similar to the Cape Town score, which recommends that LBW infants can be discharged if their score is over 16. This score contains 9 items, each of which provides 0 to 2 points (45):

- Maternal ability to appropriately position and attach the LBW infant to the breast
- Sufficient production of breast milk
- Confidence that the mother can care for her LBW infant
- Socioeconomic support
- Adequate weight gain per day
- Ability to suck
- Maternal knowledge about KMC
- Confidence in the mother to provide vitamin and iron supplements
- Acceptance of the mother to use KMC

In some hospitals, such as the Sardjito Hospital, mothers of LBW infants are also required to follow up in the lactation clinic 2 days after discharge, 1 week after the visit, and over 3 additional weekly visits. During these follow-up visits, breastfeeding and the ability to perform KMC are assessed and the infant is weighed and examined; other specialists such as an ophthalmologist, otolaryngologist, endocrinologist, cardiologist, neurologist, growth and development specialist, and surgeon are consulted if there are concerns about the infant's clinical condition. (Sardjito Hospital, unpublished report, 2016)

LBW infants who were exposed to KMC and discharged from Hasan Sadikin Hospital with continued KMC at home showed increased weight gain, maintained normothermia, and had lower risk of rehospitalization compared with LBW infants treated conventionally. (26) Continued KMC at home for more than 4 hours/day increased infant body weight by 30 g/day, which is 4 times that found when KMC was provided for less than 4 hours/day. (58)

### Early Initiation of Breastfeeding and Increased Breastfeeding Rates

Early initiation of breastfeeding was shown to reduce mortality in LBW infants in Aceh Province, Indonesia. (59) Specifically, the mortality risk decreased in neonates who received breast milk within the first hour after birth. Therefore, strategies to promote early initiation of breastfeeding are needed. (59)

The first step to improving exclusive breastfeeding rates among hospitalized infants is to increase the opportunity for mothers to have direct contact with their infants. Increased infant contact improves maternal ability to express breast milk and increases the acceptability of donor breast milk. (60) Exclusive breastfeeding in LBW infants in Indonesia was shown to reduce the risk of acute respiratory infections in the first months after birth. (61) Delayed initiation of breastfeeding or expressing breast milk for more than 6 hours and maternal need to return to work were found to be risk factors for nonoptimal breastfeeding in LBW infants. (62)

In a study comparing the growth of LBW infants in Indonesia who were fed fortified human milk versus those fed unfortified human milk, it was shown that fortified human milk was associated with better infant growth. (63) Furthermore, the improvement in growth was found in infants with birthweight between 1,000 and 1,499 g as well as those between 1,500 and 1,999 g. Better growth was achieved through higher calorie intake in the fortified human milk group. Importantly, no adverse effects were observed as a consequence of fortification of feedings. (63) For LBW infants who are not breastfed, modified postdischarge formula may serve as an alternative. (64)

### Prevention and Management of Neonatal Morbidities

**Hypothermia.** Preterm infants with LBW are susceptible to cold stress and development of hypothermia. It is therefore very important to ensure that maintenance of room temperature is part of the temperature management in preterm births.

Comparison of the effects of operating room temperatures of 75.2°F (24°C) to 78.8°F (26°C) versus 68°F (20°C) to

71.6°F (22°C) on the temperatures of LBW preterm infants have been analyzed. Randomized clinical trials were conducted from October 2016 to January 2017 in the operating room of Dr Moewardi Hospital (Surakarta, Indonesia). (65) Operating room temperatures maintained between 75.2°F (24°C) and 78.8°F (26°C) increased the median temperature of preterm infants, though the incidence of hypothermia was not different. (65) Further studies are needed to determine the ideal operating room temperatures.

**Patent Ductus Arteriosus.** In Indonesia, the incidence of a patent ductus arteriosus (PDA) in preterm infants is 14%. The presence of a PDA is more common in LBW infants. Delayed closure of the PDA is associated with the presence of respiratory distress syndrome. (66) To improve survival and reduce morbidity of premature infants in Indonesia, PDA management has become an important issue. One of the Indonesian neonatology groups is currently conducting a multicenter research trial on the interventional options for premature infants with a PDA.

**Anemia of Prematurity.** The incidence of anemia in premature infants before 4 weeks of chronologic age at Cipto Mangunkusumo Hospital (Jakarta, Indonesia) was found to be 23.9%, while the need for packed red cell transfusion was 31.3%. The higher transfusion incidence compared with anemia incidence is because some premature infants received a transfusion before the level of hemoglobin was lower than the limit of anemia defined in the study. (67) The timing of the first episode of anemia and need for a packed red cell transfusion mostly occurred in the first week after birth. Both anemia and packed red cell transfusion requirement were associated with lower gestational age, lower birthweight, a diagnosis of sepsis, longer length of stay, and discharge status against medical advice. (67)

**Indirect Hyperbilirubinemia.** In Indonesia, infants with indirect hyperbilirubinemia, a condition frequently found in LBW infants, are treated with phototherapy. In addition, a sheet of white satin that serves as a reflector is used in Indonesia to increase the effectiveness of phototherapy and lower serum bilirubin levels at a faster rate without side effects. (68)(69) One study at Kariadi Hospital (Semarang, Indonesia) found neonatal jaundice with bilirubin levels greater than or equal to 10 mg/dL (171 μmol/L) in 58.9% of LBW infants and 55.6% of preterm infants. (69) Late-onset sepsis and assisted delivery increased the risk for indirect hyperbilirubinemia. (69)

**Respiratory Support for Lung Disease of Prematurity.** Early use of a T-piece resuscitator in premature infants born in Indonesia reduced the risk of failure of CPAP by 90%. (70) The factors that influenced CPAP failure were supplemental oxygen requirement over 60% and neonatal sepsis. (70)

**Neonatal Sepsis.** Sepsis, one of the major causes of neonatal mortality, is associated with LBW, prematurity, (71)(72)(73) meconium-stained amniotic fluid, and cesarean delivery (73) in Indonesia. Gram-negative bacteria are commonly responsible for neonatal sepsis, and are associated with significant neonatal mortality. (73)

Sidauruk et al reported that at some hospitals in Jakarta, the most common organism associated with NEC was *Klebsiella pneumoniae*. (74) The authors found that the mode of delivery, length of delivery, duration of antibiotic use, and various types of nutrition did not affect the colonization of microflora in the gastrointestinal tract of patients with NEC. In 2009, 31 cases of NEC were found in 737 preterm infants at Cipto Mangunkusumo Hospital (74); the overall incidence of NEC in Indonesia has not been reported.

One study from Indonesia did not find an association of sepsis with umbilical vein catheter duration in premature infants (75) but further data are needed. The use of a closed catheter access system reduced bloodstream infections in LBW preterm infants. (76) Similar to the approach to central line use in other countries, it is important to choose a proper device design, perform proper disinfection of the device, and perform connector changes at appropriate frequency (76) to decrease the risk of line-associated infections in Indonesia.

**Retinopathy of Prematurity.** In 2006, Sitorus et al found that the incidence of retinopathy of prematurity (ROP) in preterm infants in rural Indonesia was low, but this was most likely secondary to a high mortality rate in this population. (77) Subsequent studies reported a higher incidence of ROP (including severe ROP) in infants with a birthweight less than 1,500 g (78)(79)(80)(81)(82); one study found that 17% of infants with a birthweight less than 1,000 g had ROP between stage III and stage V. (78) The overall incidence of ROP in Indonesia was higher than that found in developed countries. Importantly, in Indonesia, mild ROP is also observed in infants with birthweights of 1,500 to 2,500 g; 13% of infants with a birthweight between 1,500 and 2,000 g had stage I or II ROP and 18% of infants born over 2,000 g had stage I or II ROP. (78)

Excessive oxygen administration, regardless of mode of ventilation (eg, CPAP, intubation) is most commonly associated with ROP. (78)(80)(82)(83) The high incidence of ROP in Indonesia may be because of a less stringent control of oxygen delivery to preterm infants. Improved awareness of optimal oxygenation and better equipment to monitor oxygen delivery in Indonesia is therefore essential. (78) Other possible associations of the increased incidence of ROP include the need for blood transfusions, a diagnosis of sepsis, lower gestational age, and lower birthweight. (80)(81)

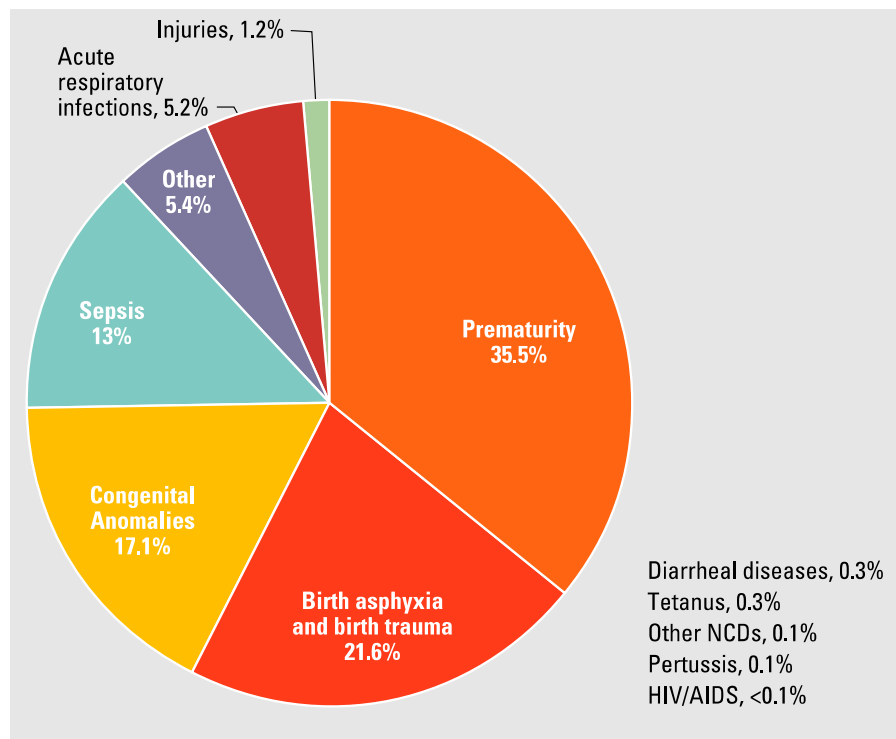
ROP screening in Indonesia can be performed at local hospitals with limited facilities. However, not all patients with severe ROP can be treated because of problems with transportation and lack of financial support. (83) Alternatives to laser therapy have also been investigated. A retrospective evaluation between August 2007 and November 2012 showed that intravitreal bevacizumab injection appeared effective in treating zone I and posterior zone II ROP, allowing for growth of peripheral retinal vessels. However, in another series of 20 treated eyes, normal vascularization of the peripheral retina was not achieved in 50% of patients. (84) As survival rates of preterm infants improve, there will be a need for better collaboration among neonatologists, specialists at tertiary care centers, and primary health care providers, providing improved referral access for high-risk premature or LBW infants. This may help pediatric ophthalmologists and retinal specialists to implement appropriate screening programs for diagnosing and treating ROP in a timely manner. (78)

**Intraventricular Hemorrhage.** Danni reported that the overall incidence of intraventricular hemorrhage (IVH) in preterm infants born at less than 35 weeks' gestation at Cipto Mangunkusumo Hospital was 43.5%. Of these infants, 7.6% had severe IVH. (85) In preterm infants born before 35 weeks' gestation, thrombocytopenia is not significantly associated with the incidence of severe IVH. (86)

## NEONATAL MORTALITY IN INDONESIA

Indonesia has a neonatal mortality rate of 14 per 1,000 live births based on data from 2015, (2) which is the 10th highest mortality rate in the world. The neonatal mortality rate is even higher if only rural births are included, estimated at 24 deaths per 1,000 live births. (2) A large portion of this mortality is related to the high prevalence of premature infants (Fig). A retrospective cohort study with data from the Indonesia Demographic and Health Survey 2007 discovered that the lower the birthweight, the lower the probability of neonatal survival. (87) This high neonatal mortality rate is expected to decrease because the number of NICUs in Indonesia has been rapidly expanding, despite limited financial support.

The prevalence of LBW remains high in Indonesia. LBW infants with neonatal sepsis have a significantly increased mortality rate. (88)(89)(90) Birthweight less than 1,000 g, Apgar score less than 4 at 1 minute of age, need for mechanical ventilatory support, sepsis, and referral to another hospital were associated with increased mortality in VLBW infants. (91) Early interventions to prevent LBW and advances in intensive care of LBW infants are recommended. (87)



**Figure.** Causes of neonatal mortality in Indonesia, 2015. (16) In Indonesia, the main causes of neonatal deaths in 2015 were prematurity (35.5%), birth asphyxia and trauma (21.6%), and congenital anomalies (17.1%).

Among the Acehnese, cultural practices such as inadequate antenatal and neonatal care, discarding of colostrum, delayed initiation of breastfeeding, and lack of exclusive breastfeeding affect outcomes. (92) Bolstering of health services both by screening for high-risk patients and tailoring interventions based on cultural practices are important to decrease neonatal mortality among LBW infants in Indonesia. (92) In addition, improving perinatal health services (ie, increased availability of skilled birth attendants and postnatal care utilization) should be considered when planning interventions to reduce neonatal mortality. (93)

## FOLLOW-UP OF LBW AND PRETERM INFANTS BORN IN INDONESIA

### Anemia

To describe iron profiles in preterm infants at 2 months' chronologic age, a cross-sectional study was conducted in infants born between 32 and 36 weeks' gestation who were followed at the Growth and Development Clinics at Cipto Mangunkusumo Hospital or Budi Kemuliaan Hospital (Jakarta, Indonesia). (94) Iron deficiency anemia was observed in 6% of infants and most of these infants had low serum iron, high total iron-binding capacity, low transferrin saturation, and low ferritin levels. (94) Most male infants with iron

deficiency anemia who had doubled their birthweight were not receiving iron supplementation and were born to mothers with low educational background as well as low socioeconomic status. (94)

### Zinc Levels

Low serum zinc levels were found in 28% of infants with birth gestational age less than 34 weeks, birthweight less than 2,000 g, and postmenstrual age greater than 35 weeks. (95) Delayed growth was the most common abnormality observed in these infants. Risk factors for low serum zinc levels included male infants, lower gestational age, decreased calcium levels, and absence of iron supplementation. (95)

### Blood Pressure and Renal Disease

LBW infants had significantly higher blood pressures than infants with normal birthweight. (96) Children who are SGA at birth have significantly higher mean homocysteine levels than those of normal birthweight. Higher homocysteine levels in children who are SGA at birth are associated with higher diastolic blood pressure. (97)

Disorders of nephrogenesis in LBW infants who were also SGA may lead to microalbuminuria and elevated blood pressures. A cross-sectional study of children aged 7 to 9 years with a history of LBW and SGA showed that the lower the birthweight, the higher the level of microalbuminuria. (98)

## Stunted Growth

Among infants born with LBW, male sex, history of neonatal illness, and poverty were associated with stunted growth at 12 to 23 months of age. (99) Of the existing variables, LBW was the most important and dominant risk factor. (99) In children aged 2 to 5 years, nonexclusive breastfeeding and LBW were significantly correlated with stunted growth. (100) Interestingly, LBW is not an important contributor to growth delay in infants born in rural areas. Because the difference in the prevalence of LBW between rural and urban communities is not significant, the difference in the prevalence of growth delay is more likely to be associated with different patterns of postnatal growth. (101)

## Development

The risk for delayed development in LBW or preterm infants increases with a diagnosis of sepsis or hyperbilirubinemia. (102) The diagnosis of SGA significantly increases the risk of developmental delays. (103) In addition to an increased risk of longer hospital stay, increased morbidity, and greater mortality, (104) late preterm infants at 3 to 6 months' chronologic age had a 4 times greater risk of delayed neurologic development compared with full-term infants. (105)

A retrospective data analysis of LBW infants with birthweights of 1,500 to 2,499 g was conducted at Hasan Sadikin Hospital from September 2003 to May 2004. Study exclusion criteria included major congenital anomalies, respiratory distress syndrome, need for mechanical ventilation, and exchange transfusion. At 7 to 10 months' corrected age, preterm LBW infants with birthweights of 1,500 to 2,499 g were noted to be at risk for developmental delay. (106) In Indonesia, long-term studies examining developmental outcomes of LBW, preterm, and SGA infants are needed as most data are based on short-term studies.

## SUMMARY

The incidence of infants with LBW, prematurity, and SGA in Indonesia remains high, and the morbidity and mortality in these infants are significant. Some of the risk factors associated with LBW, preterm, and SGA Indonesian infants are reviewed herein. The evidence-based benefits of use of KMC in this population are discussed. Although challenging, KMC is generally accepted by professionals caring for LBW infants; however, it is neither a priority in LBW health care nor is it consistently included in the structure of LBW care in Indonesia. Early initiation of breastfeeding has been shown to reduce neonatal mortality in LBW infants and improve exclusive breastfeeding rates among hospitalized

newborns; this approach needs to continue to be emphasized when caring for neonates in Indonesia.

Prematurity continues to play a major role in the increased neonatal mortality in Indonesia. Infants who do survive continue to be at increased risk for morbidities such as hypothermia, indirect hyperbilirubinemia, and sepsis. The high incidence of ROP in Indonesia may be because of less stringent control of oxygen delivery. Improved awareness of optimal oxygenation and better equipment to monitor oxygen delivery in Indonesia is crucial. It is important to follow LBW and premature infants because of the risks of various morbidities including delayed growth and development. Various patterns of postnatal growth, LBW, and non-exclusive breastfeeding were significantly correlated with growth delay. Advances in hospital care and postdischarge follow-up of LBW, preterm, and SGA infants born in Indonesia are critical to decrease the morbidities and lower the mortality associated with these populations.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Breastfeeding.
- Know the risks of neurodevelopmental impairments in term infants, late preterm infants, moderately preterm infants, and extremely preterm infants, with and without neurologic risk factors.
- Know the risk factors for and pathophysiology of retinopathy of prematurity, and approaches to prevention.
- Know the differences between physiologic and nonphysiologic jaundice.
- Know how to use a pre-discharge bilirubin measurement to predict the risk of severe hyperbilirubinemia.
- Know the clinical features of acute bilirubin encephalopathy in newborn infants.
- Control of infection.
- Know the issues in the organization of perinatal care (e.g., regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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# Maternal Mortality in the United States: Updates on Trends, Causes, and Solutions

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## ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AIM	Alliance for Innovation on Maternal Health
CARE Act	Maternal Care Access and Reducing Emergencies Act
CDC	Centers for Disease Control and Prevention
CMQCC	California Maternal Quality Care Collaborative
ICD-10	International Classification of Diseases, 10th Revision
MMR	maternal mortality ratio
MMRC	maternal mortality review committee
MMRIA	Maternal Mortality Review Information Application
MOMMA Act	Mothers and Offspring Mortality and Morbidity Awareness Act
MOMS Act	Maternal and Obstetric Modernization of Services Act
NCHS	National Center for Health Statistics
PMSS	Pregnancy Mortality Surveillance System
PQC	perinatal quality collaborative
SMM	severe maternal morbidity
WHO	World Health Organization

## Practice Gaps

1. In contrast to other high-income countries, the maternal death rate in the United States has been rising for over 20 years with persistent racial/ethnic inequities.
2. Initiatives to improve safety, quality, and equity of care during pregnancy, delivery, and beyond are essential to optimize maternal health outcomes.

## Abstract

The rising trend in pregnancy-related deaths during the past 2 decades in the United States stands out among other high-income countries where pregnancy-related deaths are declining. Cardiomyopathy and other cardiovascular conditions, hemorrhage, and other chronic medical conditions are all important causes of death. Unintentional death from violence, overdose, and self-harm are emerging causes that require medical and public health attention. Significant racial/ethnic inequities exist in pregnancy care with non-Hispanic black women incurring 3 to 4 times higher rates of pregnancy-related death than non-Hispanic white women. Varied terminology and lack of standardized methods for identifying maternal deaths in the United States have resulted in nuanced data collection and interpretation challenges. State maternal mortality review committees are important mechanisms for capturing and interpreting data on cause, timing, and preventability of maternal deaths. Importantly, a thorough standardized review of each maternal death leads to recommendations to prevent future pregnancy-associated deaths. Key interventions to improve maternal health outcomes include 1) integrating multidisciplinary care for women with high-risk comorbidities during preconception care, pregnancy, postpartum, and beyond; 2) addressing structural racism and the social determinants of health; 3) implementing hospital-wide safety bundles with team training and simulation; 4) providing patient education on early warning signs for medical complications of pregnancy; and 5) regionalizing maternal levels of care so that women with risk factors are supported when delivering at facilities with specialized care teams.



## Objectives After completing this article, readers should be able to:

1. Explain the definitions of pregnancy-related and pregnancy-associated deaths and the data challenges in the United States.
2. Recognize key contributors to rising maternal deaths and persistent inequities in the United States.
3. Identify key strategies and solutions for improving maternal health.

## INTRODUCTION

Maternal death during pregnancy, childbirth, or postpartum is a tragedy with catastrophic impact on families and serves as an important indicator of the quality of a health system. The World Health Organization (WHO) has defined maternal mortality ratio (MMR) as “the number of maternal deaths per 100,000 live births, [where] maternal death is the death of a woman while pregnant or within 42 days of termination of pregnancy,” regardless of whether the cause was related to or aggravated by pregnancy. (1) However, according to the WHO definition, maternal deaths do not include those from accidental or incidental causes. Although the MMR has been the most common indicator for international comparisons of maternal health, it does not specify the cause of death in relation to pregnancy.

The MMR in the United States has decreased drastically in the last century because of advances in surgical technique, safer anesthesia, antisepsis, and overall improved living conditions. Although the MMR dropped from 900 deaths per 100,000 live births in the 1900s to 12.7 in 2007, the US rate of MMR has seen a rise over the past several decades. (2) In 2014, complications during pregnancy, childbirth, and the postpartum period ranked as the 6th greatest cause of death among women aged 20 to 34 in the United States. (3) The MMR in the United States has more than doubled from 9.8 per 100,000 live births in 2000 to 21.5 in 2014, (4) and this trend stands out among high-income countries; maternal mortality has decreased in other high-income countries, such as Canada and the United Kingdom, during the same time period. According to the WHO, the MMR has fallen by 44% from 1990 to 2015 in low- and middle-income countries. (5)

When interpreting these trends, however, we must also account for improvements in data ascertainment. The addition of a pregnancy question on the US death certificate in 2003 coincided with increased mortality rate, which

suggests improved detection and reporting as part of the story. (4) Increasing maternal mortality rates vary by state and have generated public attention on family planning availability and the growing prevalence of chronic medical conditions including obesity, diabetes, and heart disease. Delayed childbearing leading to more advanced age during pregnancy, higher cesarean delivery rates, the opioid epidemic, and fragmented and limited access to care during and after pregnancy have also been identified as potential contributors. (6)

In the United States, the racial/ethnic inequities in maternal deaths are troubling; most notably, non-Hispanic black women carry a 3- to 4-fold risk of pregnancy-related deaths compared with non-Hispanic white women. (7) While the medical and public health communities have made strides to reduce infant mortality with strategies such as the Safe to Sleep campaign, (8) it is time to focus on solutions to improve maternal health as well, particularly for those at highest risk for adverse outcomes. This review summarizes the data collection challenges, causes of maternal mortality and severe maternal morbidity, inequities in maternal health outcomes, and solutions to reduce maternal morbidity and mortality.

## DEFINITIONS AND DATA COLLECTION CHALLENGES

In the United States, the Centers for Disease Control and Prevention (CDC) has put forward 3 classifications of pregnancy-associated death (death of a woman while pregnant or within 1 year of termination of pregnancy, irrespective of the cause)(9):

1. Pregnancy-related: “The death of a woman while pregnant or within 1 year of termination of pregnancy, from any cause related to or aggravated by her pregnancy or its management, but not from accidental or incidental causes.” (Example: the death of a woman from postpartum hemorrhage or amniotic fluid embolism).
2. Pregnancy-associated but not pregnancy-related: “The death of a woman while pregnant or within 1 year of

termination of pregnancy due to a cause unrelated to pregnancy.” (Example: the death of a pregnant woman from an earthquake).

3. Pregnancy-associated but undetermined if pregnancy-related: “The death of a woman while pregnant or within 1 year of termination of pregnancy from a cause that cannot be determined or conclusively categorized as either pregnancy-related or not pregnancy related.” (Example: a woman with an unknown mental health history dies at 6 months postpartum from a self-inflicted cause).

The CDC manages the 2 national data sources of maternal deaths: 1) the National Vital Statistics System compiled annually by the National Center for Health Statistics (NCHS), and 2) the Pregnancy Mortality Surveillance System (PMSS), a flagship program run by the Division of Reproductive Health at the National Center for Chronic Disease Prevention and Health Promotion (Table). (10) The NCHS relies exclusively on International Classification of Diseases, 10th Revision (ICD-10) codes assigned to causes of death listed on maternal death certificates and publishes the maternal mortality rate, consistent with the WHO definition of maternal death. The PMSS relies on epidemiologists to classify deaths

according to the aforementioned definitions of pregnancy-related and pregnancy-associated deaths and allocate the causes of death into 10 categories: hemorrhage, infection/sepsis, amniotic fluid embolism, thrombotic pulmonary or other embolism, hypertensive disorders of pregnancy, anesthesia complications, cerebrovascular accidents, cardiomyopathy, cardiovascular disease, and noncardiovascular medical conditions.

Measurement challenges include the limitations of ICD code accuracy and significant variation in the statewide implementation of the pregnancy checkbox on death certificates, which began in 2003, but was not fully implemented in all states until 2016. (10) Multiple studies have concluded that improvements in reporting and case ascertainment explain some of the recent increase in maternal mortality in the United States. (7)(11)(12)(13) One study estimated that about 80% of the reported increase in maternal mortality between 2000 and 2014 could be attributed to improvements in data linkages and the pregnancy box. (10) Another study found that the addition of the checkbox may have increased case identification but also misclassification, particularly among women aged 40 years or older. (14) However, after correcting for improved ascertainment of

TABLE. Sources of Maternal Mortality Information in the United States

	NATIONAL CENTER FOR HEALTH STATISTICS (NCHS)	PREGNANCY MORTALITY SURVEILLANCE SYSTEM (PMSS)
Data source	Death certificates	Death certificates linked to fetal death and birth certificates
Time frame	During pregnancy to 42 days postpartum	During pregnancy to 365 days postpartum
Source of classification	ICD-10 codes	Medical epidemiologists assign PMSS codes
Terms	Maternal death	Pregnancy-associated death
		Pregnancy-related death
		Associated but not pregnancy-related death
Measure	Maternal Mortality Rate	Pregnancy-Related Mortality Ratio
	= # of maternal deaths per 100,000 live births	= # of pregnancy-related deaths per 100,000 live births
Purpose(s)	Show national trends and provide basis for international comparison	Analyze clinical factors associated with deaths, publish information that may lead to prevention strategies
Strengths	Best source of historical data (back to 1900)	Most clinically relevant national measure of the burden of maternal deaths
	Reliable basis for international comparison	
	Based on readily available data (death certificates)	
Challenges	Constrained by ICD-10 codes	Constrained by information available on death and birth certificates
	Lacks sufficient detail to inform prevention strategies	Lacks detailed information on contributors to death

ICD-10=International Classification of Diseases, 10th Revision.  
Adapted from St Pierre et al. (80)

maternal deaths from implementation of the pregnancy question, the adjusted average MMR across 48 US states is still estimated to have risen by 27% from 18.8 to 23.8 per 100,000 live births from 2000 to 2014 (4); the smaller adjusted increase in MMR is because of significant under-reporting during the early time point. (4) The MMR in Texas doubled from 2011 to 2014, suggesting gaps in data quality rather than a true doubling of maternal death rates. (13) The study team used an enhanced method with full review of medical records for identifying pregnancy-associated deaths and found that more than half of the obstetric-coded deaths were inaccurately labeled. (13) However, even accounting for these data collection challenges, the MMR in the United States has not decreased substantially in the recent decades, as it has in other high-income countries.

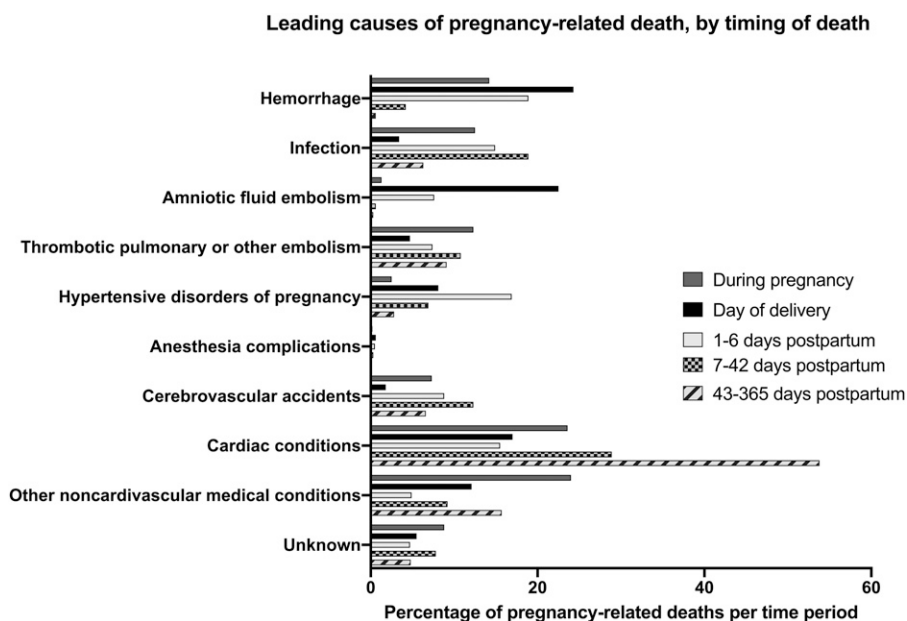
State-based maternal mortality review committees (MMRCs) are the gold standard in identifying and reviewing pregnancy-associated and pregnancy-related deaths because they are made of a multidisciplinary team that reviews all available data, including prenatal records, hospital records, and autopsy reports. (10) MMRCs are now functional in approximately two-thirds of states and are best positioned to classify deaths as preventable or not and to make recommendations to prevent similar deaths in the future. (15)(16)(17)(18)(19)(20) The CDC has developed a standardized data collection system for state MMRCs called the Maternal Mortality Review Information Application (MMRIA). (21) The MMRIA is a publicly available set of standardized

forms for abstracting data and recording MMRC decisions on 6 key questions: 1) Was the death pregnancy-related? 2) What was the cause of death? 3) Was the death preventable? 4) What were the factors that contributed to this death? 5) What are the recommendations and actions that address those contributing factors? 6) What is the anticipated impact of those actions if implemented?" (21) MMRCs play a critical role in evaluating all information about maternal deaths to identify systems solutions to improve care delivery for those that are deemed preventable.

## CAUSES OF MATERNAL MORTALITY AND MORBIDITY

The 2018 report from 9 state MMRCs concluded that around 50% of all pregnancy-related deaths were caused by hemorrhage, cardiovascular/coronary conditions, cardiomyopathy, or infection. For non-Hispanic black women, the most common underlying causes of death included pre-eclampsia, eclampsia, and embolism. For non-Hispanic white women, mental health conditions were the leading cause of death. (22)

The most recent CDC report on maternal mortality from May 2019 also identified cardiovascular conditions (including cardiomyopathy, myocardial infarction, and cerebrovascular accidents) as the cause for more than 33% of pregnancy-related deaths (Fig 1). (22)(23)(24) From 2003 to 2012 there was a 25% increase in the number of women entering pregnancy with preexisting heart disease. Most of



**Figure 1.** Leading causes of pregnancy-related death, by timing of death. Adapted from Petersen EE, Davis NL, Goodman D, et al. Vital signs: pregnancy-related deaths, United States, 2011–2015, and strategies for prevention, 13 states, 2013–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68:423–429. Note: Cardiac conditions include both cardiomyopathy and other cardiovascular disease.

these women have congenital heart disease or valvular heart disease. However, the prevalence of cardiomyopathy and pulmonary hypertension increased significantly and demonstrated the highest in-hospital mortality, most often because of heart failure, arrhythmia, respiratory failure, shock, renal failure, and preeclampsia. (25) It is unclear why the incidence of cardiomyopathy is increasing, but it could be associated with increases in maternal age, multifetal pregnancies, or improved recognition.

In a study of the National Inpatient Sample from 2002 to 2013, the incidence of cardiogenic shock (the most extreme of cardiovascular disease associated with mortality) increased over 3-fold; the mortality rate for pregnant women with cardiogenic shock was 19% compared with 0.02% of women without cardiogenic shock. (26) More than 80% of pregnant and postpartum women with cardiogenic shock had peripartum cardiomyopathy, a pregnancy-associated diagnosis that has also increased during the same period. (27) Both acute and chronic renal failure were significantly associated with mortality in women with cardiogenic shock. (26) Commonly identified risk factors for cardiovascular death include increasing maternal age, obesity, and hypertensive disorders. (27)(28) Strategies aimed at reducing modifiable chronic conditions such as obesity, hypertension, and diabetes in women of reproductive age may help reduce the incidence of cardiovascular disease and major adverse events. In addition, multidisciplinary care of pregnant women with cardiovascular disease, beginning with adequate risk assessment and evaluation for known and unknown cardiac disease is necessary to eliminate preventable maternal deaths. (29)(30)(31)

Obstetric hemorrhage was the cause of 11.5% of pregnancy-related deaths from 2011 to 2014 and is usually preventable. (32) Hemorrhage also accounts for the overwhelming majority of severe maternal morbidity, with blood product transfusions rising from 25 per 10,000 delivery hospitalizations in 1993 to 122 per 10,000 delivery hospitalizations in 2014. (24) This is a critical area for focused efforts to implement hospital-based national safety bundles, multidisciplinary team training, simulation, and reporting systems so that cases can be reviewed to ensure continuous improvement in safety and quality. (33) Successful implementation of state-wide bundles across 99 diverse hospitals in California has demonstrated reductions in severe morbidity rates from hemorrhage by 20.8%. (34) Some of the increase in prevalence of hemorrhage can be attributed to skyrocketing rates of cesarean delivery. Although cesarean can be a life-saving intervention, the US average annual cesarean delivery rate has risen from 23% in 1996 to 33% in 2011 without a corresponding reduction in maternal and

neonatal morbidity or mortality. (35) Cesarean delivery is associated with increased maternal mortality and morbidity (particularly hemorrhage, infection, and thromboembolism) compared with vaginal birth and leads to future risks for abnormal placentation such as placenta previa and placenta accreta in subsequent pregnancies. The American College of Obstetricians and Gynecologists (ACOG) has taken steps to reduce the number of unnecessary cesarean deliveries by creating guidelines for the safe prevention of the primary cesarean. (35)

Another important emerging contributor to maternal death is self-harm (suicide or accidental overdose). In Colorado, 30% of the 211 maternal deaths over a 9-year study period were related to self-harm, with the majority occurring in the postpartum period. Prior psychiatric history and psychopharmacotherapy use during pregnancy were documented in over half of these women. (36) In Philadelphia, over a 4-year period, 49% of maternal deaths had nonmedical causes, including unintentional injury (overdose, motor vehicle crash, or other), homicide, and suicide; overdose composed 40% of nonmedical causes of maternal deaths. (37) The authors caution against narrowing the focus of maternal mortality on medical causes because nonmedical causes, particularly unintentional overdose, are important contributors to pregnancy-associated mortality. Mental illness, substance use, and intimate partner violence are common risk factors among women who died of both medical and nonmedical causes, reinforcing the importance of screening and providing interdisciplinary perinatal management of substance use disorders and psychobehavioral interventions. (37)

Severe maternal morbidity (SMM) is defined by the CDC as an index of 18 indicators of significant events (such as blood transfusion, hysterectomy, heart failure, eclampsia, respiratory distress, and sepsis) corresponding to ICD-10 diagnoses during delivery admission. (24) These indicators were chosen because they can be life-threatening, and are associated with short- or long-term morbidity, prolonged hospitalization, and high health care costs. (2) Many studies of smaller datasets use SMM as a surrogate for maternal mortality because SMM is thought to include the sentinel events that lead to significantly increased risk of death. SMM rates have increased 200% from 1993 to 2014, and this increase is primarily driven by increasing blood transfusions in response to postpartum hemorrhage. After removing blood transfusion, SMM has increased 20% over this period, with hysterectomy and temporary ventilatory support accounting for the next most common complications. (24)

The prevalence of reproductive-aged women with chronic conditions continues to rise, and pregnant women

with multiple chronic conditions are at 276% higher risk of SMM and mortality than women with no chronic conditions. (38) Women with multiple chronic conditions are often older than women with a single chronic condition or no chronic conditions. Noncardiovascular medical conditions accounted for 14.3% of pregnancy-related deaths during the period from 2011 to 2015. (23)

Prepregnancy obesity has been associated with SMM and mortality in a cohort of women delivering in Washington State between 2004 and 2013, suggesting that the obesity epidemic was an important contributing factor to adverse maternal health outcomes. (39) An analysis of California births found that the incidence of SMM increased 65% from 2007 to 2014 and the prevalence of prepregnancy obesity, maternal age older than or equal to 35 years, and comorbid conditions also increased during the same period, but were estimated to contribute only 13% of the increasing morbidity. (40) Cesarean delivery was estimated to contribute 37% of the SMM in California during these 7 years. Increasing prevalence of maternal chronic medical conditions and cesarean delivery accounts for only half of the SMM, leaving room for investigation of other contributing factors. Although national efforts to reduce unnecessary cesarean deliveries may be promising interventions for reducing SMM, this study underscores the need to also address other contributing factors. (40)

In a study using delivery data from Washington State from 2000 to 2008, the rate of early-onset preeclampsia before 34 weeks' gestation increased by 33% and was associated with a 10-fold greater risk of maternal death compared with women without preeclampsia. (41) Preeclampsia is also associated with significantly higher rates of SMM, particularly from cardiovascular, respiratory, or renal failure. Hypertensive disease in pregnancy has long-term health implications, including a 2-fold increased risk for all-cause mortality before age 50 years, and increased mortality related to diabetes, ischemic heart disease, and stroke. These long-term sequelae occurred more frequently in the group of women who had 2 or more pregnancies complicated by hypertensive disease. (42) Identifying women at risk for cardiovascular disease during their childbearing years offers an opportunity to intervene and optimize long-term health.

Access to abortion care has been curtailed in multiple states because of legislative restrictions on physician and facility requirements, medication abortion restrictions, gestational age limits, funding cuts, mandatory waiting periods, and parental consent laws, which can place women at increased risk of harm if they attempt self-induced abortions. (43) Improved insurance coverage for abortion care

through state Medicaid has been associated with 16% fewer cases of SMM, suggesting that increased coverage for abortion care reduces complications associated with pregnancy. (44)

## INEQUITIES IN MATERNAL MORBIDITY AND MORTALITY

Inequities—differences that are systematic, avoidable, and unjust—in maternal health outcomes have persisted and are a cause for concern. Although multiple social conditions confer increased risk of adverse outcomes, the most prominent examples of inequities in maternal health in the United States are rooted in the social constructs of race and ethnicity. One conceptual model from Dr Elizabeth Howell demonstrates the ecosystem of factors (patient, community/neighborhood, provider, and systems) that contribute to adverse health outcomes throughout the continuum of reproductive health care, particularly for women of color. (45)

Black women experience maternal deaths at a rate 3 to 4 times that of white women in the United States, (2)(7) regardless of age. (46) According to the CDC, the pregnancy-related mortality ratios between 2011 and 2014 were as follows: 12.4 deaths per 100,000 live births for white women, 40.0 deaths per 100,000 live births for black women, and 17.8 deaths per 100,000 live births for women of other races (32); this inequity remains unchanged in the 2019 report of pregnancy-related deaths from 2015. (23) The 2018 report of 9 MMRCs revealed that greater proportions of pregnancy-related deaths of all pregnancy-associated deaths occurred among non-Hispanic black women compared with white women (Fig 2). (22)

Black and Native American women also experience increased complications from pregnancy compared with white women, regardless of socioeconomic status and

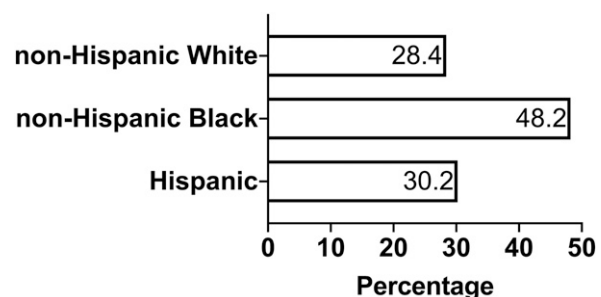


Figure 2. Proportion of pregnancy-associated deaths determined to be pregnancy-related based on race and ethnicity. Adapted from Building U.S. Capacity to Review and Prevent Maternal Deaths. (2018). Report from 9 maternal mortality review committees. [http://reviewtoaction.org/Report\\_from\\_Nine\\_MMRCs](http://reviewtoaction.org/Report_from_Nine_MMRCs). (22)

comorbidities. (47) Using 7 state inpatient databases from 2008 to 2010, Creanga et al identified race/ethnicity as an important predictor of maternal morbidity. (48) Although other factors were also identified as significant predictors of SMM, such as age less than 20 years or more than or equal to 35 years, self-pay or Medicaid coverage for delivery, low socioeconomic status, and presence of chronic medical conditions, they did not fully explain the observed racial/ethnic disparities in SMM. (48) Using the National Inpatient Sample from 2012 to 2015, Admon et al also found that SMM during delivery hospitalization was higher among all racial/ethnic groups compared with non-Hispanic whites. (49) The most common SMM was blood transfusion, which accounted for nearly 75% of all morbidity across racial/ethnic groups. The incidence of SMM was highest among women with multiple chronic conditions and particularly among those of color, suggesting increased case morbidity. (49) Grobman et al found that racial/ethnic disparities in maternal morbidity persisted even after controlling for patient-level factors and hospital of delivery. (50) In addition, racial/ethnic disparities in obstetric care delivery exist. Non-Hispanic blacks, Hispanics, and Asians all had lower odds of labor induction than non-Hispanic whites. The odds of receiving an episiotomy was increased in Asians but decreased in non-Hispanic blacks and Hispanics compared with non-Hispanic whites, (50) indicating that there may be biases in care delivery. Women of color also experience pregnancy-related complications that are associated with higher rates of death, such as tuberculosis, (51) or experience higher case fatality with conditions such as ectopic pregnancy. (52)

The root cause of racial/ethnic inequities is the legacy of structural racism that permeates people's lived experiences, including experiences in the health care system. One important driver of inequities in maternal health is distrust in the health system as a result of historical and contemporary discrimination, which often manifests as lower prenatal care utilization and adherence with treatment plans. An analysis of more than 2,000 responses to the Listening to Mothers III survey found that more than 40% of participants reported communication challenges in prenatal care and 24% perceived discrimination during birth hospitalization, predominantly among black or Hispanic women and uninsured women. (53)

Another important driver of inequities is the variation in hospital quality of care during childbirth, in which women of color more commonly go to hospitals with higher risk-adjusted morbidity compared with the hospitals where white women go more commonly. (54) In an analysis of the black-white differences in hospital of delivery in New

York City, Howell et al estimated that as much as 48% of the racial disparity in SMM could be attributed to differences in care quality at the hospital level. (55) A similar analysis among Hispanic women also showed that up to 37% of the ethnic disparity could be attributed to differences in care quality at the hospital level. (55)

Solutions to reduce inequities span all levels, from policies to address racism and social determinants of health to improving quality of care delivery and experience of care during childbirth, to mobilizing community-based organizations to support women before, during, and after pregnancy. Some examples include standardizing and improving quality of care in hospitals, particularly among facilities that have higher risk-adjusted morbidity rates and also care for a disproportionate number of women of color. (56) In addition, developing disparity dashboards to track outcomes among specific groups is important for monitoring, evaluation, and quality improvement. (57) Training on implicit bias is critical across the health care workforce to sensitize individuals to the role implicit bias may play in their interactions with patients. Lastly, there are innovative antenatal and postnatal care delivery models that are being evaluated as strategies to close disparities, such as group antenatal care and postpartum home visits with integrated interdisciplinary health teams. (58)

## IMPROVING SAFETY AND QUALITY OF CHILDBIRTH CARE

With the increases in both maternal mortality and morbidity, there has been an increasing focus on quality of care at the hospital level in the days before and after childbirth. In addition to wide variation in SMM across hospitals, there is also substantial variation within hospitals. (56) The imperative to standardize and improve safety and quality is the foundation for reducing adverse maternal outcomes in the hospital setting. The most common mechanisms to achieve this end are 1) a focus on team communication and team training; 2) implementation of evidence-based safety bundles or toolkits to manage obstetric complications that are most likely to cause SMM and/or death; and 3) data-driven MMRCs that can provide specific recommendations for systems improvement to prevent future maternal deaths.

According to a review of sentinel events reported to the Joint Commission, failures in communication were the second leading root cause of SMM and maternal mortality and the leading root cause of perinatal deaths and injuries. (59) Key facilitators include leadership champions to build and support a culture of safety that encourages open communication among all team members and transparent,



nonpunitive reporting of safety-critical events with a focus on systems improvement. (59) In addition, structured communication tools, such as safety huddles, safety checklists, “SBAR” (Situation, Background, Assessment, Recommendation) approach, and team training simulation such as TeamSTEPPS facilitate interprofessional communication and teamwork, particularly in acute situations that require coordination of resources and expertise. The maternal early warning triggers or criteria facilitate communication between bedside nurses and clinicians through increased clinical surveillance and responsiveness to patients with abnormal vital signs who may require prompt evaluation and treatment to prevent morbidity. (60)(61)(62)

Safety bundles and/or toolkits that facilitate adherence with evidence-based guidelines have been critical efforts to reduce maternal morbidity and mortality in the United States. At a national level, multiple professional organizations and stakeholders came together to form the National Partnership for Maternal Safety, which developed safety bundles for obstetric hemorrhage, severe hypertension in pregnancy, and peripartum venous thromboembolism. (63) Since the introduction of universal pneumatic compression devices at the time of cesarean delivery and rapid treatment of severe hypertension, there was a reduction in maternal deaths from postcesarean pulmonary embolism and in deaths and morbidity related to hypertensive disorders. (64)(65)(66)

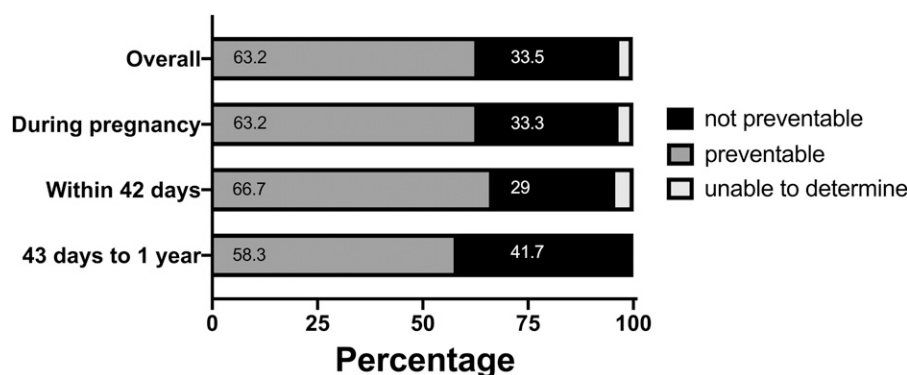
The California Maternal Quality Care Collaborative (CMQCC) was developed as a public-private partnership and leveraged data from the Department of Public Health to support data-driven large-scale quality improvement initiatives to reduce maternal deaths and morbidity. (67) CMQCC-affiliated hospitals have demonstrated reductions in maternal morbidity from postpartum hemorrhage after implementing a comprehensive hemorrhage bundle compared with non-CMQCC-affiliated hospitals in California (20.8% vs 1.2%). (34)

With federal funding from the Health Resources and Services Administration Maternal Child Health Bureau, the Alliance for Innovation on Maternal Health (AIM) was formed and led by partners from the ACOG Council on Patient Safety and Women’s Health Care and the National Partnership for Maternal Safety. (68) AIM is a state-based program that develops and provides implementation support for safety bundles. Each bundle has 4 components: readiness, recognition, response, and reporting and systems learning. (68) AIM operationalizes the bundle implementation and reporting systems through state-based teams, often organized as state perinatal quality collaboratives (PQCs). PQCs are defined as “state or multistate networks

of multidisciplinary teams, working to improve measurable population outcomes for maternal and infant health by advancing evidence-informed clinical practices and processes using quality improvement principles.”(69) The anchoring structure of PQCs relies on the department of public health, state hospital association, and clinician leadership. Additional members may include the state MMRC, community health organizations, patient advocacy groups, risk management, payers, and purchasers. (69) A critical function of the PQCs is to develop and sustain a robust data collection system for maternal health indicators at the state level.

Adjunct health system solutions to improve maternal outcomes include developing an obstetrics hospitalist workforce that may be best positioned to respond to uncommon emergencies (4)(70) and improve patient education at the time of discharge from the hospital. Although the obstetrics hospitalist workforce is growing across the United States, there remains wide variation regarding work models and scope of practice. (71) More data are needed to assess maternal outcomes in hospitals where a robust obstetrics hospitalist workforce manages intrapartum care. Similar to the integrated regional neonatal levels of care to improve perinatal mortality, maternal levels of care provide risk-appropriate care for those who would benefit from additional expertise and infrastructure because of preexisting comorbidities in pregnancy. (72) Implementation of regionalized maternal levels of care would allow for patients with high-risk conditions to be cared for at higher-volume hospitals with greater access to subspecialists. In addition, patient communication and education about danger signs, such as the POST-BIRTH tool, have been additional areas of focus to improve prompt recognition of symptoms and medical evaluation, especially once patients return home after childbirth. (73)

The 2018 report of 9 MMRCs found that more than 60% of pregnancy-related deaths were preventable and the leading factors contributing to death were patient/family factors (namely, lack of knowledge about early warning signs to seek care), provider factors (misdiagnosis or ineffective treatments), and factors related to systems of care (lack of coordination between providers) (Fig 3). (22) Most importantly, the MMRCs provided recommendations to prevent future maternal deaths, such as adopting levels of maternal care, (72) improving and enforcing policies and procedures on obstetric hemorrhage, and addressing health equity. Specifically, a California review of pregnancy-related cardiovascular deaths identified both patient and provider contributing factors, particularly a delay in patients seeking care as well as in provider response, which suggests an



**Figure 3.** Preventability of pregnancy-related deaths by time of death in analysis of 9 state maternal mortality review committees. Adapted from Building U.S. Capacity to Review and Prevent Maternal Deaths. (2018). Report from 9 maternal mortality review committees. [http://reviewtoaction.org/Report\\_from\\_Nine\\_MMRCs](http://reviewtoaction.org/Report_from_Nine_MMRCs). (22)

opportunity to improve patient education and standardize response protocols. (28)

### CURRENT HEALTH CARE POLICY TO ADDRESS MATERNAL MORTALITY

On December 21, 2018, the Preventing Maternal Deaths Act (HR 1318) was signed into law. This legislation allocates federal funding to support states in establishing and sustaining MMRCs. (74) One challenge will be standardizing data collection and reporting systems among the various MMRCs.

Other maternal health bills in Congress at this time are the Maternal Care Access and Reducing Emergencies (CARE) Act, the Rural Maternal and Obstetric Modernization of Services (MOMS) Act, and the Mothers and Offspring Mortality and Morbidity Awareness (MOMMA) Act. The CARE Act, introduced by California Senator Kamala Harris, focuses on dismantling structural racism through training programs around implicit bias for clinicians. The MOMS Act, introduced by North Dakota Senator Heidi Heitkamp, addresses the disparities in access to obstetric care for women in rural communities by creating regional networks and increasing workforce capacity in rural areas. The MOMMA Act, introduced by Illinois Representative Robin Kelly, seeks to expand Medicaid through 1 year after delivery, standardize data collection through the CDC, establish and enforce national emergency obstetric protocols, and improve culturally competent care. In addition, there are multiple bills at the state and federal levels around expanding Medicaid through 1 year after delivery and providing Medicaid reimbursement for doula services.

### PREPREGNANCY AND INTERPREGNANCY HEALTH

Pregnancy conditions, such as hypertensive disease and gestational diabetes, are known risk factors for cardiovascular disease later in life and increased early mortality. (42)(75) Other adverse pregnancy outcomes such as preterm labor and fetal growth restriction may also be associated with increased lifelong cardiovascular risk. (76) The postpartum period is a time of significant biological, psychological, and social transition with increased risk of complications, yet 10% to 40% of women do not attend any postpartum visit between 4 and 12 weeks. (77) During pregnancy and postpartum care, obstetricians have an opportunity to provide anticipatory guidance; arrange for appropriate follow-up for chronic health conditions, mental health, and substance use disorders; and identify and educate patients about early warning signs of SMM. According to the most recent CDC report, the majority of unintentional deaths occurred between 6 weeks and 1 year after delivery, highlighting the importance of the continuum of care that extends beyond the traditional 6-week postpartum period. (23) ACOG has revised recommendations for postpartum care to become an ongoing process of addressing recovery from birth, newborn care, psychosocial and sexual well-being, contraception, chronic disease management, health maintenance, and a transition to ongoing well-woman care, rather than a single encounter. (78) The prepregnancy and interpregnancy periods are windows of opportunity for implementing risk-reducing interventions for women with multiple medical conditions, mental health issues, or substance use disorders to optimize outcomes for future pregnancies and long-term well-being. Improving health systems to allow longitudinal continuous care from pregnancy and beyond is critical to reduce maternal mortality. (79)

## CONCLUSION

Pregnancy-related deaths have been steadily rising in the United States and are not just a result of improved data acquisition. Cardiovascular conditions, obstetric hemorrhage, and self-harm or unintentional harm are important causes of pregnancy-related deaths; significant inequities exist between non-Hispanic black and non-Hispanic white women. The majority of pregnancy-related deaths are preventable. Implementation of safety bundles, team training, integrated multidisciplinary care for high-risk patients, risk-stratified levels of maternal care, improvements in communication between providers and patients regarding early warning signs, and addressing structural racism and the social determinants of health are all strategies for improving maternal safety, quality and equity. Health care policy to improve funding and resources for standardized, state-based review of pregnancy-related deaths are important steps to reverse rising rates and close persistent inequities in maternal morbidity and mortality.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of maternal cardiac disease and its management.
- Know the essentials of prenatal care, including risk assessment, perinatal referral, screening, and standard monitoring.
- Know how maternal obesity may influence pregnancy and pregnancy outcome.
- Know the components of pre- and periconceptional health care (including nutritional requirements during pregnancy) that influence pregnancy outcomes.
- Know the issues in the organization of perinatal care (e.g., regionalization, transport, practice guidelines, benchmarking data, quality improvement).

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- Maternal deaths have been reported to be higher in the United States compared with similar high-income countries. The definition of maternal mortality ratio by the World Health Organization includes which of the following criteria?
  - Death must occur within 4 days of delivery.
  - If within the timeframe specified, accidental or incidental causes are still considered cases.
  - Number of maternal deaths per 100,000 live births.
  - There must be a specific cause of death identified.
  - Deaths before the third trimester are not considered cases.
- From 2000 to 2014, the maternal mortality ratio has seen a significant increase, with a doubling of the ratio. Which of the following statements regarding this observation is correct?
  - In 2014, complications during pregnancy, childbirth, and the postpartum state were the leading cause of death among women aged 20 to 34 years.
  - A similar doubling of the maternal mortality ratio has been seen in countries such as Canada, United Kingdom, and Mexico.
  - Improved ascertainment, such as by the addition of a pregnancy question on the US death certificate, may be a component of this observed increase.
  - There is a 1.5-fold higher risk of pregnancy-related deaths among non-Hispanic black women compared with non-Hispanic white women, which has persisted across this timeframe.
  - During this period, risk factors such as maternal age, body mass index, and heart disease have remained fairly stable or decreased in US childbearing women, while access to care has become more equitable and available because of health policy measures targeted toward women's health.
- A woman who was pregnant at 28 weeks' gestational age is involved in a motor vehicle accident, which was caused by the other driver being under the influence of alcohol. She sustains severe brain injury and multiorgan failure after hemorrhagic shock because of traumatic injuries from the accident. Before the accident, she had been actively receiving prenatal care, had an uneventful first trimester, and recently had been diagnosed with gestational diabetes. According to the Centers for Disease Control and Prevention, which of the following classifications would be most appropriate to characterize this death?
  - Maternal death with pregnancy-related complications.
  - Not pregnancy-associated.
  - Pregnancy-associated but not pregnancy-related.
  - Pregnancy-associated but undetermined if pregnancy-related.
  - Pregnancy-related.
- The cesarean delivery rate has increased from 23% in 1996 to 33% in 2011. Which of the following statements regarding this trend is correct?
  - This increase in cesarean delivery has been accompanied by a corresponding reduction in both maternal and neonatal morbidity and mortality.
  - During the hospitalization for childbirth, cesarean delivery has similar rates as vaginal birth in terms of maternal mortality and morbidity, with somewhat decreased incidence of hemorrhage.
  - Cesarean delivery places the woman at higher risk in future pregnancies for abnormal placentation such as placenta previa and placenta accreta.
  - The optimal rate of cesarean delivery has been determined to be 5 per 1,000 live births for optimizing maternal and neonatal outcomes, as well as cost.
  - The incidence of thromboembolism and infection is decreased with cesarean delivery compared with vaginal delivery.

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5. Variation across hospitals with regard to outcomes such as severe maternal morbidity point to opportunities for improving care. According to a review of sentinel events reported to the Joint Commission, what was the leading root cause of perinatal deaths and injuries?
- A. Failures in communication.
  - B. Maternal obesity.
  - C. Amniotic fluid embolism.
  - D. Lack of qualified physician being present.
  - E. Patient interference in care.
-

# Maternal Mortality in the United States: Updates on Trends, Causes, and Solutions

Ai-ris Y. Collier and Rose L. Molina

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# Fetal Doppler Assessment in Neonatal Care: Analysis of Fetal Doppler Abnormalities and Neonatal Outcomes

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## Education Gaps

1. There is currently no consensus on the best way to monitor fetal growth restriction. This is further evident by the limited number of studies that have investigated the association of neonatal outcomes with abnormal fetal Doppler findings.
2. The various techniques and timing of fetal Doppler assessment has created a lack of uniformity that impedes analysis of results for proper monitoring of fetal growth restriction.

## Abstract

Fetal Doppler ultrasonography provides an effective and noninvasive approach to identify circulatory abnormalities in the maternal-fetal circulation. It is invaluable to assess the hemodynamic status of the fetus under a wide range of physiologic, infectious, and abnormal anatomic conditions. Findings from these studies are often used to make clinical decisions, including whether to proceed with urgent delivery of the fetus. In this review, we focus on key literature describing the main uses of Doppler ultrasonography in neonatal medicine, including how abnormal findings may be implicated in immediate and long-term outcomes. Our review highlights the importance of fetal Doppler examination as an effective intrauterine management strategy, and its full potential is more likely to be realized when considered in context with other available clinical information.

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### ABBREVIATIONS

DV	ductus venosus
HELLP	hemolysis, elevated liver enzymes, low platelets
IUGR	intrauterine growth restriction
IVH	intraventricular hemorrhage
MCA	middle cerebral artery
NEC	necrotizing enterocolitis
PSV	peak systolic velocity
UA	umbilical artery

## Objectives After completing this article, readers should be able to:

1. Review fetal Doppler assessment relevant to neonatal care.
2. Compare different fetal Doppler studies used in neonatal health.
3. Review the association of fetal Doppler abnormalities with long-term neonatal outcomes.

## INTRODUCTION

Wavelength and frequency are 2 essential characteristics of all waves. Generally, the distance between 2 adjacent identical components of the wave is known as the

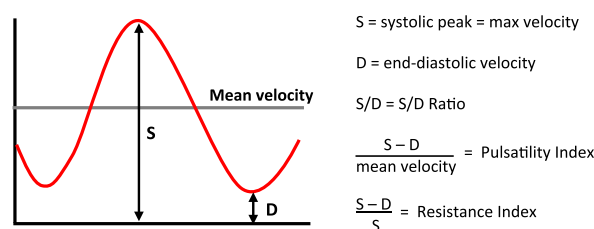
“wavelength” and the number of wave crests that transverse a single point in a second denotes “frequency.” The Doppler effect, first postulated by Christian Johann Doppler in 1842, describes the change in the observed wave frequency during relative motion between the emitting source and the receiver. For example, during the transmission of sound, if an object moves toward the listener, the frequency of the waves (pitch) increases and the frequency decreases when the object moves away from the listener. In the clinical setting, Doppler ultrasonography provides functional information about the properties of blood flow by measuring the rate of change in frequency of the sound waves deflecting off the moving red blood cells.

Methodologically, several types of Doppler ultrasound instruments are used in clinical evaluations. These include the: 1) color Doppler, which provides information on the average blood flow velocity with color codes; 2) pulse Doppler, which generates gray-scale images and graphic representation of the range of flow velocities within a sample volume; and 3) power Doppler, which identifies the amplitude of the waves, allowing better evaluation of small vessels. (1)

In 1977, FitzGerald and Drumm provided one of the earliest reports on the usefulness of ultrasound technology in the evaluation of the fetal circulation. (2) Since then, a significant number of reports have described the methodological details, crucial anatomic areas of examination, and the potential efficacy of Doppler ultrasonography during diverse pregnancy complications and disorders. (3) In addition, a number of randomized clinical trials and meta-analyses have reported on the early evaluation of maternal-fetal hemodynamics and the effect on fetal outcome.

The Figure illustrates indices based on the maximal Doppler waveform. (1) The systolic/diastolic (S/D) velocity ratio, also known as the A/B ratio, is illustrated in the Figure. (2) The pulsatility index is calculated by the systolic value minus the diastolic value divided by the mean velocity. (4) The resistance index, also known as the “Pourcelot index,” is calculated by the systolic velocity minus the diastolic velocity divided by the systolic velocity. (3)(4) The S/D ratio is the easiest measurement to use in a clinical setting, whereas the pulsatility index and resistance index are more commonly used in research studies. (4) Pulsatility index is known to be more resistant to changes in fetal heart rate variation, and is also the only index with a normal distribution. (4)

Currently, Doppler ultrasound examinations of pressure and flow velocity in the fetoplacental circulation have become an essential and integral part of perinatal surveillance, including monitoring obstetrical conditions, assessing the uteroplacental circulation, and measuring fetal hemodynamics. A diverse group of antepartum conditions predisposes the fetus to aberrant vascular physiology, which leads to a subsequent



**Figure.** Waveform of blood velocimetry. The waveform indices are shown as well as the relationships between systolic and diastolic values used in fetal Doppler analysis.

risk of developing urgent and life-threatening complications as well as long-term morbidity. These conditions include maternal hypertension, nutritional deprivation, respiratory and cardiac malformations and, more commonly, intrauterine growth restriction (IUGR). Chronic intrauterine fetal distress that can result from these conditions leads to alterations in the fetal circulation with preferential flow toward vital organs, such as the brain, heart, and adrenal glands, and away from less critical areas and organs of the body. Hence, it has been postulated that the ability of fetal ultrasonography to predict and monitor such circulatory adaptations allows for greater functionality with significant prognostic capability and clinical usefulness.

Currently, for the most part, fetal Doppler examinations focus on distinct anatomic areas and physiologic regions. These include the umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV), uterine artery, aortic isthmus, and the umbilical vein. We will describe the physiology of the UA, MCA, and DV, as these vessels are commonly evaluated in fetal medicine.

## UMBILICAL ARTERY

The UA is the most widely examined vessel in the fetal circulation. Under normal physiologic states, the UA Doppler indices are modulated by conditions such as fetal gestational age as well as fetal cardiac and respiratory functions. UA flow velocity waveforms of normally growing fetuses are characterized by low-resistance, high-velocity diastolic flow. Gestation plays a key role in the nature of the UA Doppler waveforms; as the placenta matures, the resistance in the UA decreases with increased tertiary stem villi. Technically, a number of diverse factors have been found to affect the utility and reliability of the UA Doppler index, such as the segment of the cord that is being examined, and a consistent approach is preferred (ie, evaluation at the site of insertion of cord into the placenta). (5)

Overall, UA Doppler studies have been found to be most useful in conditions of early-onset IUGR caused by uteroplacental insufficiency. (6) Increased resistance in the umbilical arterial circulation exhibiting a normal systolic to diastolic ratio, a high pulsatility index, or a very high resistance index is indicative of decreased efficiency in the placental circulation.

(7) With greater destruction of the placental villus vasculature, placental flow decreases and placental vascular resistance increases; thus, growth-restricted fetuses initially have a progressive reduction of UA diastolic flow. (8) As the placental vascular resistance increases further, the decrease in UA diastolic flow is followed by absent UA flow and, in severe cases, reversal of flow within the UA. (9) In the growth-restricted fetus, absent or reversed end-diastolic UA flow is often associated with fetal hypoxemia and acidemia, and increased perinatal morbidity and mortality. (10)

An earlier Cochrane meta-analysis of randomized clinical trials showed a clear decrease in perinatal mortality associated with the use of UA Doppler in fetuses with normal anatomy. (11) The current Society of Obstetricians and Gynaecologists of Canada guidelines on the use of UA Doppler recommend that it should not be used as a screening tool; it should be available for assessment of the fetal placental circulation where placental insufficiency is suspected; and it should be considered at the time of referral for suspected growth restriction and in follow-up for suspected placental pathology. In addition, depending on other clinical determinants, abnormal or reversed UA end-diastolic flow requires increased fetal surveillance or delivery. (12)

## MIDDLE CEREBRAL ARTERY

Characteristically, Doppler wave patterns in fetal cerebral circulation studies produce continuous forward flow in diastole and with progression of the pregnancy, the end-diastolic flow velocity increases. Indices are affected by factors including heart rate, breathing, and fetal behavior. (13) During worsening hypoxia, cerebral arterial impedance falls progressively and when eventual asphyxia occurs, no further decrease is seen. Currently, Doppler assessment of the MCA peak systolic velocity is considered to be the most effective monitoring tool for fetal anemia; an increase in MCA velocities occurs with decreased fetal hemoglobin levels. (14) It is also a useful tool in growth-restricted fetuses to assess for cerebroplacental redistribution, leading to “head-sparing” IUGR. Often, this may be the only finding in late IUGR as UA Doppler studies may be normal.

While the UA Doppler is a measure of placental function, cerebroplacental ratio studies reflect fetal consequences of increased placental resistance. Cerebroplacental ratio is calculated as the ratio of pulsatility indexes of the MCA to UA:

$$\text{Cerebroplacental Ratio} = \frac{\text{MCA Pulsatility Index}}{\text{UA Pulsatility Index}}$$

Intrauterine hypoxemia leads to cerebrovascular dilation with an associated increase in diastolic flow and a decrease

in the MCA pulsatility index. (15) Thus, a decrease in cerebroplacental ratio is indicative of fetal cerebral redistribution—a physiologic response to hypoxia. An investigation to determine if aberrant prenatal Doppler findings are predictive of postnatal abnormal autoregulation found that a lower cerebroplacental ratio is associated with abnormal cerebral autoregulation between 24 and 48 hours after birth, and predisposes infants to a higher risk of IUGR, low birth-weight, decreased Apgar scores, postnatal acidosis, intraventricular hemorrhage (IVH), and death. (15)

## DV FLOW ASSESSMENT

The evaluation of DV flow permits the most precise interpretation of fetal cardiac function as well as cardiac hemodynamics. (16) The DV has the highest forward velocity in the venous circulatory system, which facilitates detailed waveform analyses. (17) The waveform observed in the DV is characteristic of the pressure volume alterations in the cardiac atria and it is therefore highly useful in the assessment of conditions that may modify forward cardiac function. Significant impedance to flow in the DV has been shown to be associated with fetal cardiac defects and other adverse outcomes. Overall, the correlation of DV Doppler waveform with cardiac forward function makes it an indispensable tool in the evaluation of the general state of fetal cardiovascular function and risk assessment. (18) The assessment of DV velocity waveform has the potential to provide highly effective data about IUGR and studies have shown that abnormal DV Doppler flow may help to identify the optimal delivery timing in a growth-restricted fetus of more than 26 weeks' gestation. (19)

## FEEDING AND THE DEVELOPMENT OF NECROTIZING ENTEROCOLITIS

Leaf and colleagues investigated the effects of delayed enteral feeding in growth-restricted preterm infants who are at risk of developing necrotizing enterocolitis (NEC) based on abnormal antenatal UA Doppler waveforms. (20) This study included 402 preterm infants with an increased risk for NEC because they were growth restricted and had aberrant results on UA Doppler assessment. The authors found that early feeding led to shorter lengths of stay in the NICU, decreased incidence of cholestatic jaundice, and better Z scores for weight at the time of discharge, suggesting that early introduction of enteral feedings in this population does not appear to increase the risk for NEC. However, a study by Kempley et al examined the feeding and gastrointestinal effects in growth-restricted children



born at less than 29 weeks' gestation who were enrolled in the Abnormal Doppler Enteral Prescription Trial. (21) This study showed that such children with abnormal Doppler findings from the UA or cerebral redistribution failed to tolerate the trial feeding regimen. A previous study evaluated the risk of developing NEC associated with early and delayed enteral feeding in preterm growth-restricted children with abnormal prenatal UA, MCA, and uterine artery Doppler findings. (22) Findings from this study found no significant difference in the incidence of NEC between the 2 groups, suggesting that in this group of children, abnormal antenatal UA, MCA, and uterine artery Doppler results may not correlate with the risk for NEC or feeding difficulties. Manogura and colleagues investigated whether the development of NEC can be predicted based on prenatal Doppler studies in preterm infants with placental insufficiency. (23) In this study, the ability to predict NEC was assessed in 404 neonates who had prenatal UA, MCA, DV, and umbilical vein Doppler ultrasound examinations. The results showed that the infants who developed NEC had higher UA Doppler indices ( $P=.023$ ). (23) The authors concluded that placental disease plays a major role in predisposing severely growth-restricted neonates to developing NEC.

In the recent past, other prenatal Doppler ultrasonography approaches have also been evaluated for predictability of NEC in infants. Raboisson and colleagues have used intrauterine uterine artery and aortic isthmus Doppler blood flow data to examine if the risk of developing NEC can be predicted. (24) In their cohort of 123 growth-restricted fetuses, 9% developed NEC and the risk of disease development was significantly associated with bilateral notching of the uterine artery, uterine artery mean resistance index, aortic isthmus diastolic blood flow velocity integrals, and absent or negative "a" wave on the DV. In this population, it was found that uterine bilateral notching could predict NEC with a sensitivity of 83.3% and a specificity of 70.3%. (24)

## FETAL ANEMIA

In addition to infectious or inflammatory diseases, other neonatal conditions have also been studied with respect to fetal Doppler ultrasound findings. A multicenter, prospective study of 265 healthy fetuses and 113 fetuses with hemolytic disease evaluated the ability of Doppler ultrasonography to diagnose fetal anemia after maternal red-cell alloimmunization. (25) In this evaluation, an increase in the peak velocity of systolic blood flow in the MCA was found to facilitate the detection of moderate and severe anemia in at-risk children. Similarly, Simetka and colleagues studied 23

fetuses from alloimmunization pregnancies and found that those who needed postnatal transfusions for hemolytic disease had an increased progressive enhancement in MCA peak systolic velocities (MCA-PSVs) in contrast to the fetuses that did not need blood transfusions. (26) These data indicated that, in such a population, ultrasonography may help to identify those who may need postnatal transfusion therapy. Besides alloimmunization, fetomaternal hemorrhage is a well-described cause of fetal anemia that can also lead to fetal death in some cases. A review of the published literature, as well as single institution case series ( $n=3$ ), indicated that the MCA-PSV was the most effective predictor of severe fetomaternal hemorrhage. (27) The investigators recommended that an increased MCA-PSV may prompt the need for a maternal blood test to diagnose fetomaternal hemorrhage.

## NEUROLOGIC STUDIES

A commonly occurring consequence of severe placental insufficiency and the ensuing IUGR is the risk of devastating neurologic sequelae. These include conditions such as IVH and periventricular leukomalacia, which can lead to neurologic sequelae later in life. Thus, the usefulness of fetal Doppler ultrasonography to identify risk for postnatal cranial ultrasound abnormalities has been widely explored. For example, Cruz-Martinez and coworkers studied a cohort of 90 fetuses with IUGR using abnormal UA Doppler and 90 control fetuses for the prediction of postnatal cranial ultrasound abnormalities. (28) Their findings indicated that MCA Doppler is capable of differentiating subgroups with varying risks of postnatal cranial ultrasound abnormalities and that the presence of aortic isthmus retrograde net blood flow may signify a group of children with significantly increased risk of developing future central nervous system complications. However, another study of 113 growth-restricted and prematurely delivered fetuses failed to find any fetal Doppler parameter as an independent contributor to IVH. (29) Authors of this report suggested that this may be because of an actual lack of association or because of the effect of other confounding perinatal variables. Mari and coworkers examined the contribution of the brain-sparing effect, as noted by a lower pulsatility index in the MCA as an IVH risk predictor in preterm infants. (30) Findings from this study showed that fetuses with brain-sparing IUGR in the setting of maternal preeclampsia have a lower risk of developing IVH compared to those with normal cerebral artery pulsatility index and complications of preterm labor. (30)

## RESPIRATORY STUDIES

Prematurity is a well-established contributor to subsequent respiratory complications and children born extremely preterm have been shown to carry a significant burden of respiratory problems in their early life. A number of studies have examined the ability of intrauterine Doppler parameters to predict postnatal respiratory outcomes. Torrance et al evaluated the risk of respiratory distress syndrome in preterm fetuses in relation to UA Doppler findings and maternal hypertension. (31) A retrospective analysis of 187 low-birthweight infants and infants born before 34 weeks of gestation found no significant difference between those with an abnormal UA Doppler compared to those with a normal Doppler examination. (31) However, among those with abnormal Doppler findings, poorer outcomes occurred when their mothers had hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome compared to infants of normotensive mothers. The authors postulated that fetuses of women with HELLP syndrome may be more susceptible to oxidative stress, leading to lung damage.

## HEMATOLOGIC STUDIES

Another important predictor of outcome in preterm infants is the infant's hematologic profile at birth. It has been postulated that the hematologic profile at birth is a consequence of placental dysfunction and contributes to the ongoing clinical deterioration. (32) For instance, fetuses with abnormal UA Doppler findings may have platelet activation in the placental circulation, leading to thrombosis and an increased risk of thrombocytopenia. (33) A study by Baschat and colleagues found that in fetuses with IUGR, rapid and moderate deterioration was strongly associated with lower platelet counts, and moderately low platelet counts were inversely correlated with UA pulsatility index. (34)

The relationship between UA Doppler indices and the processes of vascular modeling has also been investigated. For example, angiopoietin-2, which is expressed in the first trimester, is a known regulator of placental vascular remodeling. In a study that evaluated maternal serum angiopoietin-2 levels in 11 women during first trimester screening, no relationship was noted between this protein and uterine artery notching or UA Doppler findings. (35)

## FETAL DOPPLER ABNORMALITIES WITH LONG-TERM NEONATAL OUTCOMES

The use of fetal Doppler ultrasonography to understand and predict long-term consequences, such as neurobehavioral and cognitive outcomes in later childhood, has been explored.

Such studies are also useful to identify the optimal timing for delivery, while balancing the deleterious effects of hypoxemia and acidosis that may affect the developing brain with consequences of prematurity associated with an early delivery. (36) The Growth Restriction Intervention Trial was designed to understand the optimal timing of delivery for such fetuses. (37) Pregnancies with 2 risk factors, early gestational age and abnormal UA end-diastolic flow, were evaluated in a multi-institutional randomized controlled trial. (37) If the responsible clinician was uncertain of the ideal timing of delivery, subjects were randomized to "deliver now" or "defer" until it was no longer safe to delay delivery. Findings showed total neonatal deaths before maternal discharge were 10% in the immediate delivery group compared with 9% in the delayed delivery group, suggesting insufficient evidence to prefer one approach over the other. A subsequent trial examined the long-term neurobehavioral outcomes of these patients, such as cognition, language, motor performance, and behavior at 6 to 13 years of age. (38) It was found that among the children who were examined, no significant difference was observed in cognition scores, motor scores, and parent-assessed behavior scores between the 2 groups. Also, no differences were found for odds of death or severe disability between the groups. The study authors postulated that brain injury in the immediate delivery group may balance out with advancing age because of plasticity of the developing brain, allowing for rewiring to account for imbalances.

A similar research question was recently addressed when women with growth-restricted fetuses at 26 to 32 weeks of gestation were studied to determine if the alterations in the fetal DV Doppler findings could be used to guide delivery instead of cardiotocography short-term variation, which is used to relate the activity and reactivity of the fetal heart to autonomic nervous control. (39) The outcome measures were survival without cerebral palsy, neurosensory deficits, or developmental impairments evaluated at 2 years. Findings indicated no difference in the proportion of children surviving without neuroimpairment. This study also indicated that timing of delivery using late alterations in the Doppler waveform may lead to better developmental outcomes at 2 years.

## SUMMARY

Since its first description in 1977, Doppler fetal ultrasonography during pregnancy has been studied to assess its ability to predict fetal outcomes, both in the immediate period and long term. The detected waveforms characterize the alterations in the Doppler signal generated by the interaction of

the ultrasound frequency with the blood in targeted blood vessels. Factors influencing the readings include fetal cardiac activity, density of the blood, elastic properties of the vessel wall, and peripheral resistance. (39) Currently, the Doppler fetal ultrasound approach offers a safe and non-invasive modality to investigate fetal hemodynamics and well-being. These studies inform clinicians about the status of the uteroplacental circulation. A significant amount of information is gained about the fetoplacental circulation by Doppler examination of the UAs. In addition, flow indices of the MCAs provide information about fetal anemia, hypoxemia, and acidosis. Additional data can also be gained on critical diagnoses such as NEC, alloimmunization, and critical hematologic indicators of the fetus to make timely clinical decisions. However, detailed review of the available literature also indicates, in many cases, that there is a lack of consensus as to the most effective way to interpret the data to monitor fetal growth restriction. A lack of uniformity in the techniques used in the various studies also impedes the interpretation and comparative analyses of the data. In many of these reports, critical information, such as the interval between the Doppler examination and delivery, are not provided or not standardized. In summation, fetal Doppler technology is an extremely valuable tool for providing effective maternal and fetal care, and its full potential is likely to be realized when the findings are interpreted and used in conjunction with other clinical information.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow measurements, in assessment of fetal conditions and well-being.

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1. Fetal Doppler ultrasonography is routinely used in clinical practice to monitor fetal well-being and evaluate for the presence of obstetrical complications. Which of the following statements regarding the principles of Doppler ultrasonography is correct?
  - A. Doppler ultrasonography assesses blood flow properties by measuring changes in the wavelength of the sound waves deflecting off moving red blood cells.
  - B. Color Doppler techniques are used to measure average blood flow velocity using color codes.
  - C. Power Doppler techniques are used to assess the amplitude of sound waves in large vessels.
  - D. Pulse Doppler generates gray-scale images depicting the range of wave amplitudes in a sample volume.
  - E. The Doppler effect was first described by Christian Johann Doppler in 1942.
2. Preferential distribution of flow toward vital organs such as the brain can be observed in fetuses exposed to chronic intrauterine stress. Fetal Doppler ultrasonography allows clinicians to monitor these circulatory adaptations as well as predict the development of life-threatening complications and need for delivery. Which of the following conditions has NOT been linked to alterations in fetal circulation?
  - A. Cardiac malformations.
  - B. Maternal hypertension.
  - C. Respiratory malformations.
  - D. Maternal anemia.
  - E. Intrauterine growth restriction (IUGR).
3. Fetal Doppler examination of the umbilical artery (UA) has been the most commonly used method to study fetal circulation. In healthy fetuses, UA diastolic flow velocity waveforms are characterized by low resistance and high velocity. In contrast, decreased, absent, or even reversed end-diastolic flow can be observed in fetuses with IUGR. Which of the following statements regarding the clinical usefulness of Doppler UA studies in growth-restricted fetuses is correct?
  - A. Fetal hypoxemia and acidemia have been shown to occur in fetuses with reversed end-diastolic flow, but not in those with absent end-diastolic flow.
  - B. Decreased efficiency in placental circulation should be suspected in fetuses with a low UA resistance index.
  - C. The use of UA Doppler in healthy fetuses has been shown to decrease perinatal mortality.
  - D. Fetuses affected by uteroplacental insufficiency have a decreased systolic to diastolic ratio.
  - E. Doppler UA studies are most useful in late-onset IUGR compared with early-onset IUGR.
4. Middle cerebral artery (MCA) flow is characterized by continuous diastolic forward flow with increase in end-diastolic flow velocity with advancing gestation. MCA velocity is primarily regulated by fetal hemoglobin and  $P_{CO_2}$ , not  $P_{O_2}$ . Which of the following statements regarding Doppler assessment of MCA flow patterns is correct?
  - A. MCA peak systolic velocity is the most effective tool for monitoring fetal anemia.
  - B. In growth-restricted fetuses with head sparing, alterations in MCA peak systolic velocity are a late finding, often not seen until alterations in UA Doppler indices are detected.
  - C. The cerebroplacental ratio is calculated as the ratio of pulsatility indices of the MCA to ductus venosus.
  - D. In response to hypoxia, the cerebroplacental ratio increases, indicating physiologic fetal cerebral redistribution of blood flow.
  - E. Altered cerebroplacental ratio is associated with abnormal cerebral autoregulation in the first 12 hours after birth.

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5. Multiple studies have investigated the usefulness of fetal Doppler ultrasonography to predict later neonatal outcomes such as necrotizing enterocolitis (NEC), cranial ultrasound abnormalities, and risk of hematologic abnormalities. Which of the following statements regarding fetal Doppler ultrasonography and development of significant perinatal complications is correct?
- A. A history of abnormal antenatal UA Doppler indices is typical in growth-restricted infants who later develop NEC.
  - B. Aortic isthmus retrograde net blood flow is one of the fetal Doppler parameters studied to predict later NEC risk.
  - C. The most predictive parameter of severe fetomaternal hemorrhage is MCA peak systolic velocity.
  - D. The UA pulsatility index is positively correlated with risk of moderate neonatal thrombocytopenia, with higher UA pulsatility index corresponding to higher postnatal platelet counts.
  - E. Some investigators have found that increased MCA pulsatility index is associated with risk of intracranial hemorrhage in preterm infants.



# Fetal Doppler Assessment in Neonatal Care: Analysis of Fetal Doppler Abnormalities and Neonatal Outcomes

Nadia Narendran and Kamran Yusuf

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# Update on Prenatal Laboratory Screening: Joint Commission Required Elements

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## Practice Gaps

Although prenatal screening for infectious diseases is part of routine prenatal care in the United States, many women do not receive adequate prenatal care, or screening is inadequate during this care. In support of recommendations from the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics, the Joint Commission recently issued new requirements mandating hospitals that offer obstetric services to carefully evaluate select maternal infectious disease status at the time of admission to the labor and delivery department, and document these results in both the maternal and neonatal medical record.

## Abstract

The Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics recommend routine screening for pregnant women for evidence of infection with human immunodeficiency virus, hepatitis B and syphilis, and vaginal-rectal colonization with group B *Streptococcus*. For each of these pathogens, there are important opportunities to provide maternal treatment, prevent vertical transmission of the pathogen during the prenatal or intrapartum periods, and/or administer neonatal treatment immediately after birth. Such prevention and/or treatment measures are critical to limiting maternal and neonatal morbidity; however, this is dependent on recognition of maternal disease status. A significant number of women in the United States receive either inadequate prenatal care or inadequate screening for these pathogens. The time of admission to labor and delivery units represents an important opportunity to detect at-risk pregnant women and infants. To optimize both maternal and neonatal health, the Joint Commission issued new guidance effective July 1, 2018, mandating documentation of maternal disease status for these pathogens in the maternal medical record and documentation of positive results in the newborn medical record. Immediate peripartum testing for women with inadequate screening is also required. These measures should allow for timely interventions to improve maternal health and ideally to prevent perinatal disease transmission to the newborn.

**AUTHOR DISCLOSURE** Drs Teppar and Puopolo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
CDC	Centers for Disease Control and Prevention
GBS	group B <i>Streptococcus</i>
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus

## Objectives After completing this article, readers should be able to:

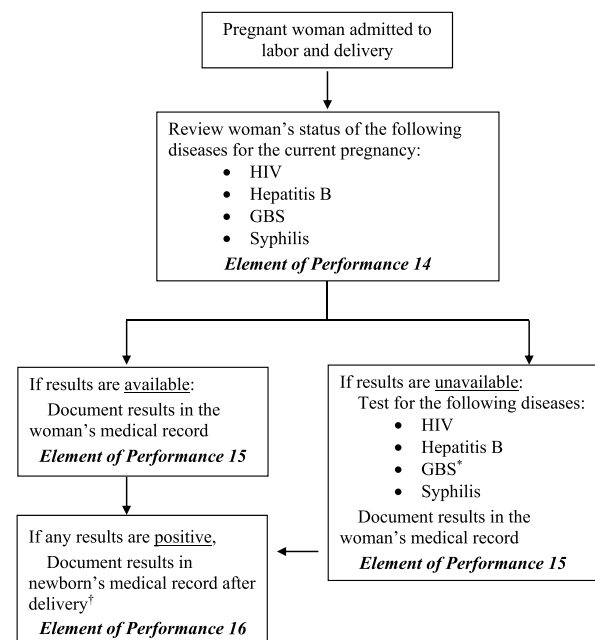
1. Recognize that the evaluation of antenatal maternal status relating to human immunodeficiency virus, hepatitis B, group B *Streptococcus* and syphilis is required by Joint Commission standards.
2. Recognize that the documentation of test results on admission to the labor and delivery department is critical for timely maternal and neonatal interventions for these infections.

## INTRODUCTION

Vertical transmission of infection from the pregnant woman to the fetus has long been a concern of both obstetric and neonatal clinicians. Detection, maternal treatment, and prevention of vertical transmission of infection has become one of the core principles of prenatal and perinatal care, and is particularly important for human immunodeficiency virus (HIV), hepatitis B virus, group B *Streptococcus* (GBS), and syphilis. Although many women are screened during pregnancy, evaluation at the time of admission for delivery is also important because 15% of women in the United States receive inadequate prenatal care and 1.6% of women do not receive any prenatal care. (1) In 2014, approximately 75% of pregnant women in the United States were tested for HIV before delivery and only 36% of surveyed hospitals had policies in place to test women with undocumented HIV status at the time of delivery. (2) In addition, among commercially insured pregnant women from 2011 to 2014, approximately 82% were tested for hepatitis B and 85% were tested for syphilis. (3)(4) The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and the American Association of Pediatrics (AAP) all currently recommend that every pregnant woman be evaluated for adequate screening for these pathogens when admitted to labor and delivery units.

In response to these recommendations, the Joint Commission instituted new requirements for accredited hospitals that offer obstetric services, specifically labor and delivery services. Effective July 1, 2018, 3 new elements of performance were added to Joint Commission Standard PC.01.02.01 in the Provision of Care, Treatment, and Services chapter of the hospital accreditation manual. (5) These requirements are an effort to improve identification of pregnant women who have not been screened

appropriately, as well as facilitate timely testing and treatment for mothers and neonates who have not received adequate screening or for neonates whose mothers have tested positive for these conditions. The requirements are summarized in the Figure. In this review, we will describe the rationale for testing, and briefly examine the



**Figure.** The Joint Commission Provision of Care Standard PC.01.02.01. \*Because GBS test results may not be available for 24 to 48 hours, organizations may elect not to perform this test but instead administer prophylactic antibiotics to the pregnant woman. †Some electronic health record systems are programmed to automatically transfer this information from the pregnant woman's record to the newborn's record; however, this is not always the case. The organization must have a process to ensure that this information is documented in the newborn's medical record. GBS=group B *Streptococcus*; HIV=human immunodeficiency virus. Data used with permission from Maternal infectious disease status assessment and documentation standards for hospitals and critical access hospitals: R3 report—requirement, rationale, reference. Available at: [https://www.jointcommission.org/r3\\_issue\\_12/](https://www.jointcommission.org/r3_issue_12/). (5)

interventions used to prevent perinatal transmission for each of the pathogens tested.

## HUMAN IMMUNODEFICIENCY VIRUS

HIV can be transmitted to the fetus or newborn at any time during pregnancy, childbirth, or breastfeeding. Before the development of effective intrapartum HIV prophylaxis strategies, approximately 25% of infants born to mothers with HIV acquired the infection. (6) With prevention strategies, the number of perinatal transmissions to persons born in the United States has declined to 1.7 per 100,000 live births in 2010 and 1.3 per 100,000 live births in 2015. (7)

Although most perinatal transmissions occur during the intrapartum period, identification of maternal HIV infection as early as possible in pregnancy is beneficial to both pregnant women and newborns. Recognition of infection allows for maternal evaluation and initiation of treatment with antiretroviral therapy as early as possible in the pregnancy. This is beneficial to the woman's health; furthermore, decreasing maternal HIV viral load before delivery significantly decreases the risk of perinatal HIV transmission. Lack of antenatal testing is associated with increased risk of perinatal transmission. To improve screening rates, the CDC and ACOG recommend an opt-out approach to HIV testing, whereby the obstetric clinician should notify the woman that she will be tested for HIV using a combination antibody-antigen test as part of routine initial prenatal testing unless she declines screening. Repeat HIV testing in the third trimester, preferably before 36 weeks of gestation, is recommended for women with an initial negative HIV test result but who are deemed to be at high risk of acquiring HIV infection. (8) High-risk criteria are shown in Table 1.

For women without prior screening or with otherwise unknown disease status, testing with a rapid HIV screening test at the time of admission to labor and delivery is recommended. Fourth-generation assays that include early antigen as well as antibody detection are optimal for the detection of very early infection. All reactive rapid tests should be confirmed with definitive supplemental testing, though initiation of antiretroviral therapy should not be delayed while awaiting these results. If results of both tests are positive, HIV RNA testing should be performed to guide decisions regarding mode of delivery. (8)(9) Any infant born to a woman with unknown HIV status at the time of delivery should be immediately tested.

TABLE 1. **Risk Criteria for Repeat Third-Trimester HIV Testing**

HIGH-RISK CRITERIA
Diagnosis of another sexually transmitted disease within the prior 12 months
Use of intravenous drugs or sexual intercourse with a person using intravenous drugs
Sexual intercourse with a new partner or >1 partner during the current pregnancy
Partner with known HIV diagnosis or at high risk for acquiring HIV
Receipt of care at facilities with an annual HIV incidence $\geq 1$ case/1,000 pregnant women
Residence in geographic locations with high population incidence of HIV infection
Current incarceration
Demonstration of signs or symptoms of acute HIV infection <sup>a</sup>

HIV=human immunodeficiency virus.

<sup>a</sup>Symptoms of acute HIV infection include fever, lymphadenopathy, skin rash, myalgias, arthralgias, headache, oral ulcers, leukopenia, thrombocytopenia, transaminase elevation.

Data from Committee on Obstetric Practice, HIV Expert Work Group. ACOG Committee Opinion No. 752: Prenatal and perinatal human immunodeficiency virus infection testing. *Obstet Gynecol*. 2018;132(3):e138–142. (8)

Opportunities exist to decrease the risk of perinatal HIV transmission during prenatal, intrapartum, and postnatal care. Detection of HIV infection via routine first trimester screening can afford the benefit of early maternal treatment with antiretroviral medications with the goal to consistently suppress the viral load to less than 1,000 copies/mL. A viral load that is less than 1,000 copies/mL is associated with a perinatal transmission risk of less than or equal to 1% to 2% regardless of route of delivery or duration of rupture of membranes. (9) Women who have already been placed on an effective combined antiretroviral therapy should continue their regimen during the intrapartum period. (7) It is unclear whether intravenous zidovudine is useful in this scenario and this can be ordered at the clinician's discretion. For women not in labor and with no rupture of membranes, if the viral load is greater than 1,000 copies/mL or is unknown, a scheduled cesarean delivery at 38 weeks' gestation is recommended. These patients should receive intravenous zidovudine, starting at least 3 hours preoperatively. For women who are in labor or have ruptured membranes with a viral load greater than 1,000 copies/mL or have an unknown viral load, it is unclear whether there is benefit to urgent cesarean delivery. (9)

In the postpartum period, women in the United States should be advised not to breastfeed. In contrast, the World Health Organization supports breastfeeding of infants in low-resource settings given the competing health risks of formula feeding. Ongoing research is addressing the safety of breastfeeding when maternal treatment achieves undetectable viral load. (7)(10) Neonates should be tested via HIV RNA or DNA detection, as antibody tests will be inaccurate because of the presence of maternal antibodies. (7) Infants born to HIV-infected mothers require different postnatal treatment depending on maternal treatment and testing, and infant test results. Neonatal therapies should be started as soon as possible after birth and at least within 12 hours of birth, emphasizing the importance of prenatal testing and the availability of rapid peripartum testing when appropriate prenatal testing has not been done. Infants born to mothers receiving stable HIV treatment with undetectable viral loads may receive zidovudine monotherapy for 4 to 6 weeks. (7) Infants born to women with detectable viral loads who are receiving antiretroviral treatment, or those born to women not yet treated, will require different treatment approaches, including multidrug prophylaxis; for newborns at highest risk of acquisition, multidrug empiric treatment regimens are provided. (7) Consultation with pediatric infectious disease specialists is required to establish the optimal treatment and testing approach.

## HEPATITIS B VIRUS

Hepatitis B is most often transmitted to the fetus at the time of labor and delivery. In the absence of timely treatment, perinatal infection can occur in up to 30% of infants born to mothers who are only hepatitis B surface antigen (HBsAg) positive and in approximately 85% of infants born to mothers who also are hepatitis B e antigen (HBeAg) positive. (10) Perinatal infection is accompanied by a chronic hepatitis B infection rate of approximately 90%, which historically has been associated with a 25% lifetime risk of death from hepatocellular carcinoma or liver cirrhosis. (11) Recent advances in antiviral therapy as well as the effectiveness of perinatal prophylaxis mandate screening for hepatitis B infection to ensure optimal care for the pregnant woman and to prevent infection in the newborn.

Pregnant women should be screened routinely at the first prenatal visit by testing for HBsAg. Women at high risk for infection are similar to those at high risk for HIV; criteria for repeat testing in the third trimester or at admission for delivery are listed in Table 2. (11) Women who test positive for HBsAg should then be tested for HBeAg, hepatitis B

TABLE 2. **Risk Criteria for Repeat Third-Trimester Hepatitis B Testing**

### HIGH-RISK CRITERIA

Diagnosis of another sexually transmitted disease within the prior 12 months
Use of intravenous drugs or sexual intercourse with a person using intravenous drugs
Sexual intercourse with a new partner or >1 partner during the current pregnancy
Household or sexual contact of HBsAg-positive persons
Coincident HIV infection
Chronic liver disease or end-stage renal disease
International travel to regions with HBsAg prevalence $\geq 2\%$
Demonstration of signs or symptoms of acute hepatitis

*HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus. Reprinted with permission from Centers for Disease Control and Prevention. Screening pregnant women for hepatitis B virus (HBV) infection. Available at: <https://www.cdc.gov/hepatitis/hbv/pdfs/PrenatalHBsAgTesting.pdf>. (13)*

virus DNA, and alanine aminotransferase. (12) All women who are found to be HBsAg positive should be referred to a gastrointestinal specialist for further care. The presence of HBeAg, viral load greater than 20,000 copies/mL, and evidence of an elevated alanine aminotransferase are all reasons for immediate referral. Depending on the results of the specialist evaluation, hepatitis B antiviral therapy may be initiated during pregnancy, particularly for women with very high viral loads.

Neonatal immunization with a single-antigen hepatitis B vaccine and administration of hepatitis B-specific immunoglobulin is the primary method to prevent perinatal transmission. The AAP issued a policy statement in 2017 addressing strategies for prevention of perinatal transmission of hepatitis B infection; this statement supports the updated recommendations of the Advisory Committee on Immunization Practice. (10) The policy statement contains a management algorithm addressing clinical scenarios (Table 3). Further vaccination and serologic confirmation of immunity should be guided by birthweight and maternal infection status (6)(10):

- All infants with birthweight greater than or equal to 2,000 g should complete a 3- or 4-dose vaccine series as recommended.
- Infants with birthweight less than 2,000 g born to HbsAg-positive mothers should routinely complete a 4-dose vaccine series.



TABLE 3. Preventative Measures for Perinatal Hepatitis B Infection

MATERNAL TEST RESULT	INFANT BIRTHWEIGHT	RECOMMENDATION
HBsAg positive	All birthweights	Hepatitis B vaccine and HBIG within 12 hours of birth
HBsAg negative	<2,000 g	Hepatitis B vaccine at 1 month of age or before hospital discharge (if prior to 1 month)
HBsAg negative	≥2,000 g	Hepatitis B vaccine within 24 hours of birth for all medically stable infants
HBsAg unknown	All birthweights	Hepatitis B vaccine within 12 hours of birth
HBsAg unknown	<2,000 g	HBIG within 12 hours of birth if mother's test status remains unknown by 12 hours of age
HBsAg unknown	≥2,000 g	HBIG within 7 days of birth or at hospital discharge (if prior to 7 days of age) if mother's test status remains unknown

HBsAg=hepatitis B surface antigen; HBIG=hepatitis B immunoglobulin.

Reprinted with permission from Committee on Infectious Diseases; Committee on Fetus and Newborn. Elimination of perinatal hepatitis B: providing the first vaccine dose within 24 hours of birth. *Pediatrics*. 2017;140(3):pii: e20171870. (10)

- All infants born to HbsAg-positive mothers (and those whose maternal status remains unknown) should have postvaccination serologic testing 1 to 2 months after the final vaccine dose to confirm immunity. If anti-HbSAg antibody levels are less than 10 mIU/mL, further vaccination with a single additional vaccine dose or a full repeat vaccine series should be administered, followed by repeat serologic testing.

Even with appropriate administration of perinatal prophylaxis, ~1% of infants born to infected mothers acquire perinatal hepatitis B infection, usually in the setting of high maternal viral load. (13) Recent studies have evaluated the use of antiviral therapy in the third trimester combined with standard newborn prophylaxis to reduce perinatal transmission in women with very high viral loads. The availability, efficacy, and safety of such treatment provide additional rationale for routine prenatal testing for hepatitis B infection. (14)(15)(16)

#### GROUP B STREPTOCOCCUS

GBS (*Streptococcus agalactiae*) is a gram-positive diplococcus that remains the most common bacterial cause of neonatal early-onset sepsis, as well as a significant cause of maternal peripartum infection. (17)(18) Approximately 20% to 25% of women in the United States are GBS colonized in their gastrointestinal and/or genitourinary tracts during pregnancy. Perinatal transmission of GBS nearly always occurs at the time of labor and delivery, although rarely, in utero infection may be noted before the onset of delivery and can cause stillbirth. Appropriate

intrapartum antibiotic prophylaxis administered to women colonized with GBS is associated with an approximately 90% decrease in the risk of neonatal GBS disease. (19) Maternal GBS colonization status is also one of the key variables considered by neonatal clinicians when assessing an infant's risk for neonatal early-onset sepsis after birth. (20) Therefore, optimal disease prevention management depends on the timely knowledge of maternal colonization and appropriate communication of these results to the clinicians managing maternal labor and delivery and inpatient neonatal care.

Since 2002, universal antenatal screening of pregnant women for GBS colonization has been recommended by the CDC, ACOG, and AAP to prevent early-onset neonatal GBS infection. Recently updated guidelines for screening and intrapartum management are summarized in Table 4. Clinicians are encouraged to review the 2019 ACOG and AAP revised guidelines for complete maternal and neonatal management recommendations. (21)(22)

Penicillin G and ampicillin remain the most effective medications for intrapartum antibiotic prophylaxis. Clindamycin and vancomycin are not as effective as  $\beta$ -lactam antibiotics in preventing neonatal GBS disease; (19) further, the CDC Active Bacterial Core Surveillance system demonstrates that 40% to 45% of GBS isolates are currently not susceptible to clindamycin. (23) Women with a history of penicillin allergy should ideally have formal allergy testing during pregnancy to confirm this history, as studies demonstrate that fewer than 10% of such allergies are confirmed. (24)

TABLE 4. **Guidelines for GBS Screening and Intrapartum Antibiotic Prophylaxis**

#### RECOMMENDATIONS FOR GBS SCREENING

- Pregnant women should routinely be screened for GBS colonization at 36 0/7–37 6/7 weeks' gestation using vaginal-rectal culture–based microbiologic methods
- Pregnant women who present with preterm, prelabor rupture of membranes or concern for preterm labor should be screened for GBS colonization at the time of presentation using vaginal-rectal culture–based microbiologic methods
- Pregnant women who present at  $\geq 37$  0/7 weeks' gestation in labor with unknown GBS status may be screened with rapid NAAT if available
- Pregnant women who present in labor at any gestational age with *negative* GBS culture results more than 5 weeks old should undergo a repeat culture and be treated as GBS unknown until repeat culture results are available

#### Exceptions to GBS Screening

- Pregnant women in whom any colony count of GBS bacteriuria had been identified at any point during pregnancy *should be considered GBS-positive* and do not require screening at 36–37 weeks' gestation
- Pregnant women with a prior infant who suffered GBS infection *should be considered GBS-positive* and do not require screening at 36–37 weeks' gestation

#### Administration of IAP

Maternal Status	Recommendation
GBS-positive	<ul style="list-style-type: none"> <li>• Administer IAP during labor</li> <li>• IAP does not need to be administered if delivery is by cesarean section AND before the onset of labor AND rupture of membranes at the time of delivery</li> </ul>
GBS unknown	<ul style="list-style-type: none"> <li>• Administer IAP if any of the following are present: <ul style="list-style-type: none"> <li>◦ gestational age <math>&lt; 37</math> 0/7 weeks</li> <li>◦ maternal intrapartum temperature <math>\geq 100.5^{\circ}\text{F}</math> (<math>38^{\circ}\text{C}</math>)</li> <li>◦ duration of rupture of membranes <math>\geq 18</math> hours</li> <li>◦ NAAT positive for GBS</li> <li>◦ NAAT negative for GBS but risk factors are present</li> </ul> </li> <li>• Consider administering IAP if the woman was known to be GBS-positive in prior pregnancy and woman and clinician agree</li> </ul>

#### Recommended Antibiotics for GBS IAP

Penicillin G	Preferred antibiotic unless woman is allergic to penicillin
Ampicillin	Acceptable alternative antibiotic unless woman is allergic to penicillin
Cefazolin	Antibiotic for women with penicillin allergy without concern for anaphylaxis
Clindamycin	Antibiotic for women with penicillin allergy with concern for anaphylaxis <i>if</i> GBS colonizing isolate is known to be susceptible to clindamycin
Vancomycin	Antibiotic for women with penicillin allergy with concern for anaphylaxis <i>if</i> GBS colonizing isolate is known to be non-susceptible to clindamycin or if susceptibility data are not available

GBS=group B Streptococcus; IAP=intrapartum antibiotic prophylaxis; NAAT=nucleic acid amplification test.

Reprinted with permission from Prevention of Group B streptococcal early-onset disease in newborns: Committee Opinion No. 782. Obstet Gynecol. 2019;134(1):e19–e40 (21); and Puopolo KM, Lynfield, R, Cummings JJ; Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of infants at risk for group B streptococcal disease. Pediatrics. 2019; 144 (2): e20191881. (22)

## SYPHILIS

Syphilis infection is caused by the spirochete *Treponema pallidum*. The infection is characterized by 4 distinct stages in the absence of effective treatment. Primary infection is characterized by the presence of painless mucosal ulcers, often in the perineal region; the secondary stage is notable for a characteristic rash, lymphadenopathy, and often systemic, flulike

symptoms. Latent infection, in which serologic evidence of infections is seen in the absence of symptoms, can persist for years. The tertiary stage of syphilis can occur years after the initial infection and can be marked by cardiovascular, hepatic, and central nervous system injury. Perinatal syphilis is most commonly transmitted transplacentally, but it can also be transmitted at the time of labor and delivery from contact with infectious lesions. Fetal infection is associated with high

rates of miscarriage, in utero fetal death, or stillbirth. The risk of transmission of syphilis is related to the clinical syphilis stage and is highest for primary and secondary syphilis. (6)(25) Therefore, detection of maternal syphilis as early as possible is critical for maternal, fetal, and newborn health.

Typically, prenatal screening for syphilis is performed using a nontreponemal test such as the VDRL or rapid plasma reagin tests; if a screening result is positive, a reflex treponemal test, typically a fluorescent treponemal antibody–absorbed test, should be performed to confirm the diagnosis. Syphilis screening should be performed at the first prenatal visit. Women at high personal risk for infection (similar to those at risk for HIV and hepatitis B; see Tables 1 and 2) and all women who live in communities where the prevalence of syphilis is high should have repeat screening at 28 to 32 weeks of gestation and again at the time of admission to labor and delivery. (26)

Women with syphilis diagnosed during pregnancy should be staged and treated appropriately according to CDC guidelines. (26) Penicillin G is the only effective treatment that can be administered during pregnancy to treat the woman, prevent fetal infection, and/or treat fetal infection. Women with a history of penicillin allergy should undergo formal allergy testing and desensitization therapy if an allergy is confirmed. Women diagnosed with syphilis in the second and third trimesters of pregnancy should have ultrasound examinations to assess for signs of fetal infection, including thickening of the placenta, fetal anemia, or signs of fetal hydrops; a maternal-fetal medicine consultation should be obtained if there is concern for fetal infection.

The evaluation for syphilis in the newborn is complex, and is informed by maternal screening results; adequacy of maternal treatment, if given, and evidence of maternal serologic response to that therapy; clinical evaluation of the neonate for signs and/or symptoms of congenital syphilis; and comparison of maternal and neonatal nontreponemal titers after delivery. The AAP *Red Book* provides detailed neonatal management algorithms. Neonatal clinicians should consult the *Red Book* for updated management recommendations in all cases of confirmed or suspected maternal syphilis infection during pregnancy. (25)

## Summary

- A significant number of pregnant women receive inadequate screening for HIV, hepatitis B virus, and syphilis infection, and for GBS colonization.
- Multiple opportunities exist for treating maternal infection and preventing perinatal transmission for each of these pathogens, but all are dependent on timely recognition of maternal infection or colonization.

- Pregnant women should be tested for HIV, hepatitis B, and syphilis infection at the first prenatal visit. High-risk criteria for each infection vary, but when present, rescreening should be done in the third trimester and/or at presentation for delivery.
- GBS vaginal-rectal culture is routinely performed at 36 0/7 to 37 6/7 weeks of gestation, unless there is a history of GBS bacteriuria during the current pregnancy or a prior neonate with early-onset GBS disease.
- Assessment of maternal testing for HIV, hepatitis B, GBS, and syphilis at the time of admission to labor and delivery provides an opportunity to initiate screening if testing is inadequate, and to repeat testing if indicated.
- The Joint Commission standards require documentation of indicated HIV, hepatitis B, GBS, and syphilis testing in the maternal medical records on presentation for delivery and in the neonatal medical record after birth.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the rationale for, and approaches to, screening for maternal Group B Streptococcal colonization during pregnancy.
- Know the management and complications of perinatal infections with *Treponema pallidum*.

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## Update on Prenatal Laboratory Screening: Joint Commission Required Elements

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# Index of Suspicion in the Nursery

## 1 Apnea and Hypotonia in a 1-month-old Infant

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### PRESENTATION

A 33-day-old male twin presents with apnea. He was delivered at 34.3 weeks by a 30-year-old gravida 6 para 4, aborta 1 woman with negative serologic findings. Her prenatal course was complicated by maternal urinary tract infection treated with antibiotics. The neonate was delivered vaginally at 34.3 weeks and required a 12-day stay in the NICU to establish feedings before being sent home. During the week leading up to apnea at home, he was found to have congestion, increased drooling, and decreased stools. He was feeding less and required syringe feedings. On the day of presentation he was found to have apnea requiring cardiopulmonary resuscitation. He was brought to the children's hospital emergency department. All other review of symptoms was negative.

In the emergency department, the infant is noted to have global hypotonia with weak cry, diminished suck, and grasp reflexes. The rest of the examination findings are normal. He has another episode of apnea and bradycardia requiring intubation and admission to the NICU. During his NICU stay, he remains globally hypotonic with no purposeful movements or reflexes.

### DIFFERENTIAL DIAGNOSIS

Differential diagnosis for an infant with hypotonia is broad, including congenital myopathies, neuromuscular disease, metabolic disease, central nervous system disorders, connective tissue disease, and infection.

### NICU COURSE

During his NICU stay, he remained globally hypotonic with no purposeful movements or reflexes. He received an extensive evaluation for hypotonia. An evaluation for infection, including respiratory viral panel, blood, urine, and cerebrospinal fluid culture, was negative. Antibiotics were discontinued after 48 hours given the negative cultures. Comprehensive metabolic panel and thyroid studies were all within normal range. Cerebrospinal fluid neurotransmitters were remarkable for low free  $\gamma$ -aminobutyric acid. Urine toxicology screen was positive for lidocaine. Imaging including computed tomography of the head and skeletal survey were all within normal limits. Brain and spine magnetic resonance imaging with spectroscopy was remarkable for symmetric increased T2 signal within the cord corresponding to lateral corticospinal tracts. Electroencephalography showed nonspecific encephalopathy with discontinuous immature pattern. Electromyography showed

**NOTE** The editors and staff of *NeoReviews* find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in *NeoReviews* when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

**AUTHOR DISCLOSURE** Dr Castro has disclosed that she serves on the advisory boards of Biogen and Sarepta and receives research grants from Biogen, Sarepta, Reveragen, and Fibrogen. Drs Hoge, Thomas, Hanners, and Ali have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

global prolonged onset motor response and severely decreased amplitude and moderately decreased conduction velocity. Repetitive stimulation of nerves was unable to be completed because of minimal motor responses. Given the history of congestion, constipation followed by descending paralysis, and negative findings on evaluation, clinical suspicion for infant botulism became high, and it was arranged for the infant to receive infant botulism immunoglobulin (BabyBIG) before stool toxin test result was obtained. Within a week of receiving BabyBIG, the infant's tone markedly improved. He underwent extubation 1 week after the administration of BabyBIG and began tolerating full oral feeds. He was discharged from the hospital tolerating full feeds by mouth and with mild hypertonia that later spontaneously resolved in follow-up clinic. Stool toxin tests later had a positive result for botulinum toxin B and small amounts of botulinum toxin F.

## INFANT BOTULISM

Infant botulism is a rare but life-threatening condition caused by a neurotoxin released from *Clostridium botulinum*, which is classified as a spore-forming, obligate anaerobic gram-positive bacillus. The neurotoxin inhibits the cholinergic neuromuscular junctions of striated and smooth muscles as well as tear, salivary, and sweat glands; this leads to symptoms of generalized weakness, constipation, and inability to tolerate secretions, often confused for upper respiratory symptoms in children. There are 8 different known botulism toxins, toxins A through H. Toxins A, B, E, and rarely, F, G, and H cause human disease. Toxin F is known to have a rapid onset, whereas the others have a more insidious onset. The toxins can be found in foods such as honey or canned items and dust or soil worldwide. The toxin can be acquired through eating contaminated foods, breathing contaminated dust, puncture wounds, or injection drugs with contaminated needles. To diagnose the disease, a high clinical suspicion is needed and the California Department of Health can be contacted for dispersion of BabyBIG. A stool sample should be sent for the toxin, but results take time, and treatment with BabyBIG should not be delayed if the clinical history fits with the signs of botulism. BabyBIG acquired from California does not include immunoglobulins against toxin F; therefore, if no improvement is seen with California's BabyBIG, the Centers for Disease Control and Prevention can be contacted to inquire for botulinum toxin F immunoglobulins with cases with a positive stool sample. A clinical response to the immunoglobulins should be seen within 1 week, with complete recovery seen within 2 to 3 weeks. This is in contrast to spontaneous resolution in a period of 6 weeks to months over the natural history of the disease if patients remain on

life-sustaining support, mainly respiratory support. BabyBIG therapy therefore can decrease morbidity, costs, and mortality.

## Lessons for the Clinician

- Infantile weakness and hypotonia have a broad differential.
- Infantile botulism is rare, but given the correct clinical history and examination findings, it should be considered in the differential diagnosis.
- When a diagnosis of infantile botulism is made, BabyBIG therapy can save lives and costs.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.
- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Know the epidemiology and pathogenesis of clostridial infections including *Clostridium botulinum*, *Clostridium difficile*, and *Clostridium tetani*.
- Know the prevention of clostridial infections including *Clostridium botulinum*, *Clostridium difficile*, and *Clostridium tetani*.
- Know the clinical manifestations, diagnostic features, management, and complications of clostridial infections including *Clostridium botulinum*, *Clostridium difficile*, and *Clostridium tetani*.
- Know the indications for and limitations of various neurodiagnostic tests.
- Know the significance of persistent neuromotor abnormalities in infancy (including asymmetries).
- Control of infection.

## Suggested Readings

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## Case 1: Apnea and Hypotonia in a 1-month-old Infant

Margaret "Katie" Hoge, Jennifer Muncy Thomas, Natasha Wyndham Hanners, Diana Patricia Castro and Noorjahan Ali

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# Index of Suspicion in the Nursery

## 2

## Abdominal Distention in a Term Infant with Unilateral Ventriculomegaly

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### PRESENTATION

An early term female neonate is born at 37 weeks, 2 days of gestation with a birthweight of 3.1 kg. She is delivered vaginally by a 26-year-old woman after induction of labor for preeclampsia with severe features; magnesium sulfate was given during labor. Prenatal history is significant for late prenatal care (14 weeks) and fetal diagnosis of right-sided ventriculomegaly noted on serial ultrasonography, first at 20 weeks of gestation and confirmed on fetal magnetic resonance imaging (MRI) at 27 weeks. All prenatal serologic findings were negative, a 1-hour oral glucose tolerance test result was within normal limits, and cell-free fetal DNA was negative for trisomies 13, 18, and 21. Maternal-fetal medicine, neonatal-perinatal medicine, and pediatric neurosurgical physician teams were involved in the prenatal care, and a plan was developed to admit the infant to the level III NICU after birth for further brain imaging.

At delivery, the infant is vigorous, with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. Birthweight is at the 50th percentile, length is greater than the 97th percentile, and occipitofrontal circumference is at the 90th percentile. The remainder of the newborn examination is unremarkable, including a perforate anus, and the infant is admitted to the NICU for known right-sided ventriculomegaly. On the day of birth, postnatal MRI demonstrates asymmetric right-sided ventriculomegaly likely secondary to a prior germinal matrix and intraventricular hemorrhage. The infant feeds orally and voids normally but no stools are noted. At birth, a chromosomal microarray is obtained, which later reveals a likely benign duplication at 7q21.12-7q21.13, with no known clinical significance associated.

On the day after birth, the infant develops abdominal distention with decreased bowel sounds and lethargy. Oral feeding is discontinued and intravenous fluids are initiated. Vital signs are stable and examination findings are otherwise unremarkable, with no respiratory distress noted in room air. Voiding remains normal, but again, no stools are noted.

### CASE PROGRESSION

A kidney, ureter, bladder (KUB) radiograph was obtained, which demonstrated mildly dilated loops of bowel throughout the abdomen. The infant was given nothing by mouth, and a Replogle tube was placed for abdominal decompression. Intravenous antibiotics (ampicillin and gentamicin) were started after performing a sepsis screen. The complete blood cell count and C-reactive protein levels were unremarkable. A repeat KUB radiograph remained concerning for a small bowel

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obstruction (Fig 1), and the infant developed bilious output from the appropriately positioned Replogle tube. A water-soluble contrast enema was performed on the third day, which revealed multiple intraluminal filling defects and meconium plugging (Fig 2). Shortly after the contrast enema, the infant began to pass stools, with 5 large-volume meconium stools noted in the following 24 hours. Abdominal distention and gastric output decreased, and a repeat KUB radiograph demonstrated decreased gaseous distention. Oral feedings were reinitiated 2 days after the enema and were advanced without difficulty. Daily occipitofrontal circumference measurements remained stable throughout the infant's hospitalization. She was discharged from the hospital on the 7th day after birth, voiding and stooling appropriately, and with follow-up scheduled with the neurosurgical team to continue to monitor the stable ventriculomegaly.

## DISCUSSION

The differential diagnosis of abdominal distention in a newborn includes volvulus (with or without malrotation), necrotizing enterocolitis, sepsis, Hirschsprung disease, meconium syndromes (such as ileus or plug), intestinal webs or atresias, hypertrophic pyloric stenosis, congenital microcolon, spontaneous intestinal perforation, imperforate anus, peritoneal bands, internal hernias, and rarely, lactobezoars. (1)(2) Small left colon syndrome, first described

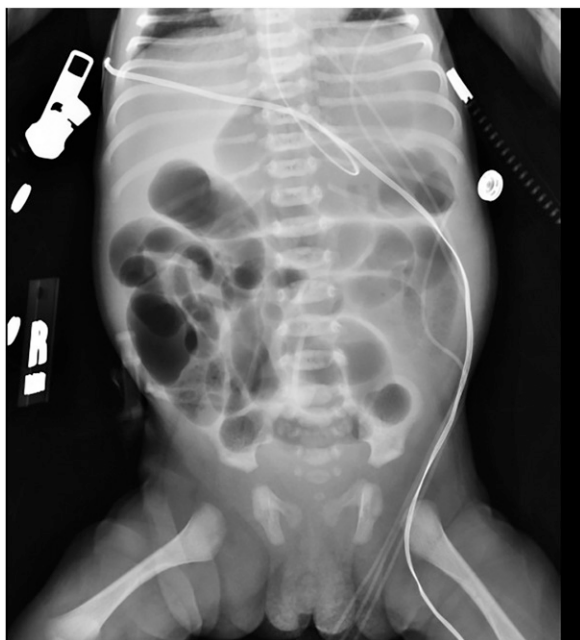


Figure 1. Small bowel obstruction noted on repeat kidney, ureter, bladder radiograph.



Figure 2. Multiple intraluminal filling defects and meconium plugging noted on water-soluble contrast enema.

in 1974, is thought to occur because of immaturity of the myenteric plexus ganglia (1) of the colon, which leads to a transient functional obstruction in newborns and carries a strong association with maternal diabetes mellitus, (3)(4) maternal preeclampsia treated with magnesium sulfate, (1) and prematurity. (1) Maternal diabetes mellitus, either gestational or pregestational, is the most common association, reported in 40% to 50% of the few published cases of small left colon syndrome. (3) Small left colon syndrome is the most common diagnosis in newborns who fail to pass meconium within the first 48 hours after birth. (1)(3)(4)(5)(6)

Abdominal radiography will demonstrate lower bowel obstruction with or without air-fluid levels. Water-soluble contrast enema is frequently both diagnostic and therapeutic in these patients, demonstrating a significant change in colonic caliber. An abrupt transition occurs at the splenic flexure to a narrow distal colon, relieving the obstruction by flushing away any meconium present in the distal colon. Normal intestinal motility without long-term complications is expected in cases of neonatal small left colon syndrome.

## Lessons for the Clinician

- Delayed passage of meconium can be associated with disorders such as Hirschsprung disease; however, small left colon syndrome is the most common diagnosis.
- Small left colon syndrome carries a strong association with maternal diabetes mellitus.



- Any newborn who does not pass meconium within the first 48 hours after birth should have a prompt evaluation for obstruction, even if asymptomatic.
- Water-soluble contrast enemas are frequently both diagnostic and therapeutic in these patients.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Identify the developmental pattern for motility of various segments of the alimentary canal.
- Know the factors that may inhibit or improve intestinal motility.

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# Index of Suspicion in the Nursery

## 3 Hydrops Fetalis, Pancytopenia, and Hemolytic Jaundice in a Preterm Neonate: A Diagnosis Made After 3 Months

Viraraghavan Vadakkencherry Ramaswamy, MD, DM (Neonatology), DNB (Neonatology),\* Gajanan Venkat Rao, MD,\* Nori Suryanarayana, MD,\* Pavan Kumar Darisi, DCH,\* Sanghamitra Gummadapu, MD, DM (Neonatology)\*

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### PRESENTATION

A 33-week-gestation female neonate with a birthweight of 1,920 g is born via vaginal delivery to a primigravida woman who is blood group A positive. She is referred to the NICU 1 hour after birth as a case of antenatally diagnosed hydrops fetalis.

#### Admission to 44 Hours After Birth

The newborn has stable vital signs with no respiratory distress or circulatory insufficiency. She is pale, with a distended abdomen, and tense on palpation. Ultrasonography reveals significant ascites with no pleural or pericardial effusion. A complete blood cell (CBC) count reveals anemia with a hematocrit of 30%. The total leukocyte count, absolute neutrophil count, and platelet count are within normal reference ranges for gestational age. Direct Coombs test (DCT) result is negative. A provisional diagnosis of hydrops fetalis with anemia is rendered, and congenital parvovirus infection is considered as a strong possibility.

#### 44 to 96 Hours After Birth

The neonate develops indirect hyperbilirubinemia with a total serum bilirubin value of 15 mg/dL (256.5  $\mu$ mol/L) with a further drop in hematocrit to 26%. The CBC count reveals new-onset thrombocytopenia, with a platelet count of  $50 \times 10^3/\mu$ L ( $50 \times 10^9/L$ ), leukopenia with a total leukocyte count of  $3,600/\mu$ L ( $3.6 \times 10^9/L$ ), and neutropenia with an absolute neutrophil count of  $800/\mu$ L ( $0.80 \times 10^9/L$ ). The peripheral smear shows red blood cells (RBCs) with 12% reticulocytes, fragmented cells, spherocytes, target cells, and anisopoikilocytosis. Both white blood cells and platelets are also reduced in the peripheral smear. Results of both the DCT and the indirect Coombs test are negative. The neonate is treated with phototherapy, packed blood cell transfusion, and intravenous antibiotics for suspected sepsis. Septicemia or a nonimmune hemolytic disorder is strongly suspected.

#### 96 Hours After Birth to Day 14

Phototherapy is stopped at 96 hours and restarted after 24 hours because of rebound hyperbilirubinemia and continued until day 8. Most of the blood reports are available. Blood culture report is sterile and antibiotics are stopped 48 hours after initiation. Glucose-6 phosphate dehydrogenase (G6PD) level is 19 U/g of hemoglobin, which is normal. Osmotic fragility for hereditary spherocytosis is normal and further testing is planned. Hereditary pyropoikilocytosis and elliptocytosis are ruled out based on the peripheral smear report. Tandem mass spectroscopy shows no abnormal results for galactosemia or other

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inborn errors of metabolism. Blood group incompatibility for Rh C, E, and Kell antigen is negative. Testing for toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections is not suggestive. Blood tests for parvovirus immunoglobulin (Ig) M and DNA polymerase chain reaction (PCR) are negative. Urine testing for glycosaminoglycans for mucopolysaccharidosis is negative. Pancytopenia improves and all blood tests reach normal limits by day 14. The neonate is discharged by day 15 after birth. At the time of discharge, minimal ascites is present. The parents are advised to follow up with a plan for further evaluation for hereditary spherocytosis.

### 3 Months Post Natal Age

The infant's mother is admitted to an intensive care unit with fever, pallor, and thrombocytopenia. Her sensorium deteriorates and she receives mechanical ventilation. Neuroimaging reveals subdural hemorrhage. Her blood reports and bone marrow biopsy findings are consistent with systemic lupus erythematosus (SLE) with autoimmune hemolytic anemia and thrombocytopenia. The antinuclear antibody profile is strongly positive. Similar to the newborn, her DCT result is negative. Further testing, including DCT with RBCs washed with normal saline at 39.2°F (4°C) detects low-affinity IgG. The mother's sample, which had been stored at the time the infant was symptomatic, is positive for antinuclear antibodies. A retrospective diagnosis of neonatal lupus erythematosus with hydrops fetalis, pancytopenia, and hemolytic jaundice is made. At follow-up, the infant is growing well and developmentally normal. The CBC count repeated at age 3 months is normal, with no anemia, leukopenia, or thrombocytopenia. Ultrasonography of the abdomen reveals no ascites. The liver function test results are normal.

## DISCUSSION

This was a case of neonatal lupus erythematosus that presented with immune hydrops fetalis with pancytopenia and hemolytic jaundice. Many of these mothers whose infants are affected are asymptomatic (~40%) and can develop manifestations of SLE later. (1) Neonatal lupus erythematosus can have varied presentations, from being asymptomatic in most cases to hematologic manifestations such as anemia, leukopenia, or thrombocytopenia to neonatal hepatitis or complete heart block. (1)(2)(3)(4) Cimaz et al, in a case series of 124 pregnancies with mothers affected with SLE, found the incidence of various hematologic abnormalities to be 27%. (5) Similar to our case, there are reports of neonatal lupus presenting without the classic skin rash or heart block.

The incidence of DCT-negative hemolytic anemia in the adult population is anywhere from 3% to 11%. (6) There

are many reasons for the DCT to be negative: 1) it could be because of the presence of IgG molecules on the RBCs at a lower density, which could not be identified by the commercial anti-IgG agent; or 2) it could be because of the presence of low-affinity IgG, which is removed while the RBCs are washed at 98.6°F (37°C). (6) The latter cause was responsible in the current case. The low-affinity IgG molecules were not specifically sought by washing the RBCs with cold saline at 4°C. Because the result of the DCT was negative, maternal SLE, which is a cause of autoimmune hemolytic anemia as well as pancytopenia in the newborn period, was not considered, and hence the diagnosis was missed. The low-affinity IgG coating the RBCs was detected in the mother at the time her general condition deteriorated. Her antinuclear antibodies were positive, thus confirming SLE. The blood samples of the mother, which were stored at the time of the infant's symptoms, tested positive for antinuclear antibodies, and the DCT conducted on the infant's RBCs revealed low-affinity IgG antibodies. Hence, a retrospective diagnosis of neonatal lupus erythematosus was made.

### First Diagnosis

The presence of hydrops fetalis with anemia, with negative results on DCT pointed to a diagnosis of congenital parvovirus. However, DNA PCR for parvovirus was negative.

### Second Diagnosis

The onset of pancytopenia with raised bilirubin level and negative results on DCT suggested an infective pathophysiology that could either be neonatal bacterial sepsis or TORCH infections. It could also be neonatal bacterial sepsis in an infant with an underlying condition predisposing for nonimmune hemolytic anemia (hereditary spherocytosis/elliptocytosis/pyropoikilocytosis), minor blood group incompatibility, G6PD deficiency. However, the tests for all of these conditions were negative.

### Final Diagnosis

Clinical deterioration in the mother requiring intensive care unit admission and the subsequent diagnosis of SLE with immune hemolytic anemia and thrombocytopenia pointed to a similar autoimmune pathophysiology responsible for the development of hydrops fetalis with pancytopenia and immune hemolytic jaundice in the infant in the neonatal period. The blood tests were conclusive and a diagnosis of neonatal lupus erythematosus with immune hydrops and pancytopenia with hemolytic jaundice (caused by low affinity IgG) was made after a period of 3 months.

### Lessons for the Clinician

- Neonatal lupus erythematosus should be considered in the differential diagnosis for immune hydrops fetalis.

- In the presence of a peripheral smear showing a hemolytic pattern, the possibility of an immune hemolytic anemia should be considered even when the DCT result is negative.
- Diagnosing an asymptomatic mother whose infant has neonatal lupus erythematosus might be life saving for the mother herself in the future.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes of and diagnostic approach to an infant who is anemic at birth.
- Know the etiology and pathophysiology of hemolytic anemias in the neonate.

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## Preterm Premature Rupture of Membranes with Recurrent Variable Decelerations

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

**AUTHOR DISCLOSURES** Drs Nguyen and MacGregor have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	≥−10
Mixed acidosis	<7.20	>60	Variable	≥−10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

### Baseline Variability

- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:  
Absent: Amplitude range is undetectable  
Minimal: Amplitude range is greater than undetectable to 5 beats/min  
Moderate: Amplitude range is 6–25 beats/min  
Marked: Amplitude range is >25 beats/min

### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes

- May be episodic (occurs without a contraction) or periodic

### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

### Interpretation

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia

- Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability
  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
    - Absent variability with any of the following:
      - Recurrent late decelerations
      - Recurrent variable decelerations
      - Bradycardia
    - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## CASE PRESENTATION

A 22-year-old gravida 2, para 1-0-0-1 woman at 27 weeks and 4 days of gestation dated by 7-week ultrasonography was transferred from an outside hospital with preterm premature

rupture of membranes (PPROM). She received prenatal care in another state and was visiting family at the time of this admission. She reported that she initially had previable PPROM at 18 weeks' gestation in her home state. She stopped leaking fluid and had normal amniotic fluid volumes following that period, suggesting that the membranes had resealed. She was treated expectantly and scheduled for routine obstetrical follow-up. She continued her pregnancy without leakage of fluid until 2 days before this admission. She denied contractions and vaginal bleeding, and reported normal fetal movement.

Her obstetrical history included a term vaginal delivery of an appropriate-for-gestational age infant in May 2018. She conceived 4 months after delivery of her first child. Her medical history was significant for hypothyroidism, which was well-controlled with levothyroxine. Her surgical history was negative.

On admission, the patient was afebrile (97.7°F [36.5°C]) with a heart rate of 56 beats/min, respiratory rate of 18 breaths/min, and blood pressure of 114/57 mm Hg. On speculum examination, she had pooling of fluid that was positive on testing for nitrazine, ferning and immunoassay (Amnisure, Qiagen). She did not have any vaginal bleeding, and the cervix appeared closed visually. She was not examined digitally. A group B *Streptococcus* (GBS) culture was positive, and gonorrhea, chlamydia, and urine cultures were all negative. She had mild leukocytosis of  $12.2 \times 10^3/\mu\text{L}$  ( $12.2 \times 10^9/\text{L}$ ).

She was admitted to the antepartum service for PPROM. She received magnesium sulfate ( $\text{MgSO}_4$ ) for fetal neuroprophylaxis for 12 hours, latency antibiotics for 7 days, and betamethasone for fetal lung maturity. She underwent an ultrasound evaluation. The fetus was in a cephalic presentation and the amniotic fluid index was 5.26 cm with the deepest vertical pocket measuring 2.47 cm. The estimated fetal weight was 921 g, consistent with the 32nd percentile for gestational age. Throughout her admission she remained afebrile. The initial FHR tracing is shown in Fig 1.

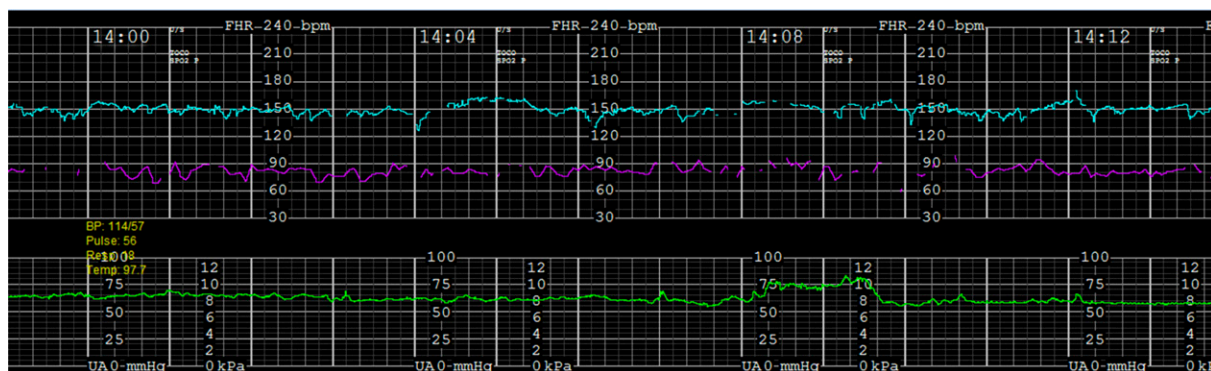


Figure 1. Electronic fetal monitoring strip 1: tracing on hospital day 1.

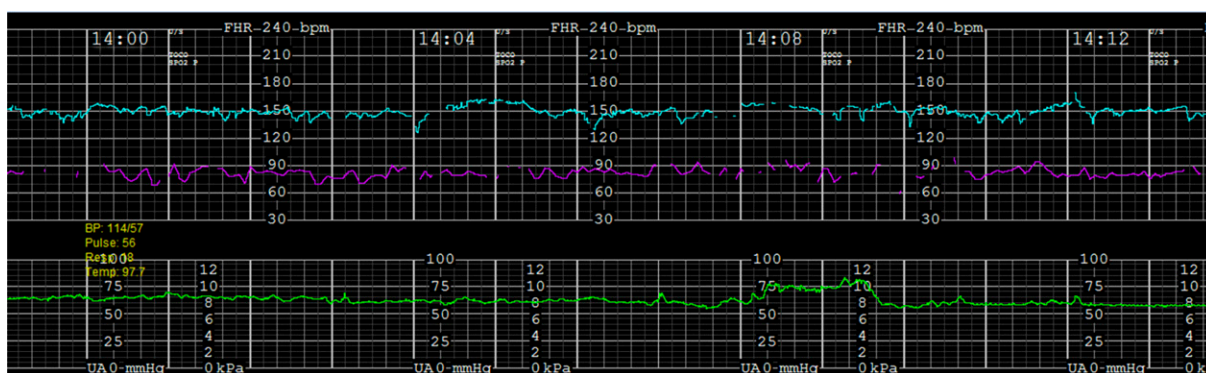


Figure 1. Electronic fetal monitoring strip 1: tracing on hospital day 1.

Findings in EFM strip 1 are as follows (Fig 1).

- Variability: Moderate.
- Baseline: 150 beats/min.
- Episodic pattern: Greater than 10×10 accelerations.
- Uterine contractions: None.
- Interpretation: Category I tracing.
- Differential diagnosis: Normal oxygenated infant of less than 32 weeks' gestation.
- Action: Admit patient to antepartum service for PPRM.

On hospital day (HD) 4, she had blood-tinged vaginal mucous after voiding. The speculum examination revealed no active bleeding. She continued to have pink-tinged scant

leakage of fluid. On HD 8, she passed a dime-sized blood clot without contractions. On HD 16 at 29 weeks and 6 days of gestation, she complained of bright red bleeding without contractions. She underwent an ultrasound evaluation, with estimated fetal weight of 1,136 g (12th percentile) and amniotic fluid index of 5.8 cm. On HD 19, she had bright red vaginal bleeding without contractions. On HD 21, the patient complained of increasing leakage of fluid and pelvic pressure. On HD 24, the patient had active bleeding and was brought to the labor and delivery (L&D) department for monitoring because of concern for possible placental abruption. The FHR tracing at that time is shown in Fig 2.

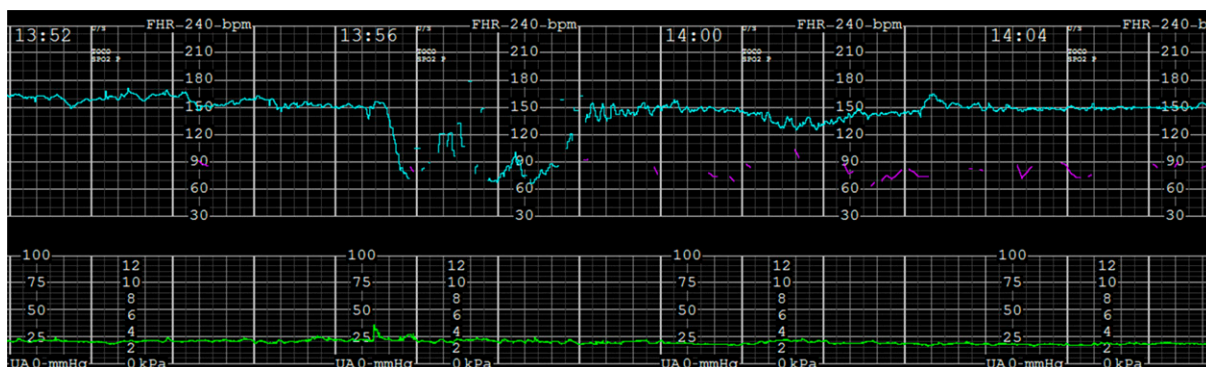


Figure 2. Electronic fetal monitoring strip 2: tracing during antepartum evaluation on hospital day 24.



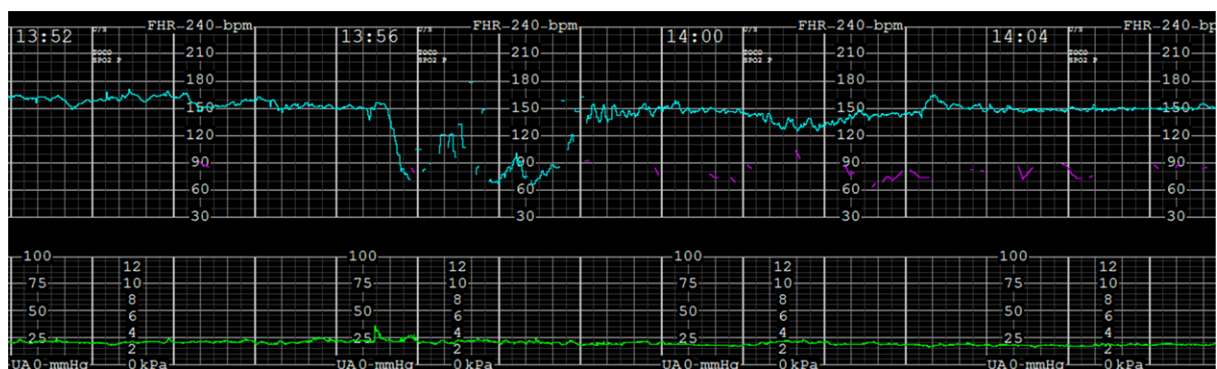


Figure 2. Electronic fetal monitoring strip 2: tracing during antepartum evaluation on hospital day 24.

Findings in EFM strip 2 are as follows (Fig 2).

- Variability: Moderate.
- Baseline: 150 beats/min.
- Episodic pattern: 2-minute deceleration with nadir at 70 beats/min; recovery to baseline of 150 beats/min, with moderate variability without accelerations; this was followed by a variable deceleration 2 minutes later, lasting 1.5 minutes with nadir of 125 beats/min and return to baseline of 150 beats/min with minimal variability.
- Uterine contractions: None.
- Interpretation: Category II tracing.

- Differential diagnosis: Cord prolapse, cord compression, uteroplacental insufficiency, placental abruption.
- Action: Repositioning, hydration, patient brought to L&D for monitoring.

MgSO<sub>4</sub> treatment for neuroprophylaxis was reinstituted, and she was given ampicillin because of her GBS-positive status and a rescue course of steroids. She had an estimated blood loss of 200 mL while being monitored. Fetal monitoring showed recurrent variable decelerations (Fig 3). Her hemoglobin was 14.9 g/dL (149 g/L) with platelets of  $165 \times 10^3/\mu\text{L}$  ( $165 \times 10^9/\text{L}$ ) and fibrinogen of 543 mg/dL ( $15.9 \mu\text{mol/L}$ ).

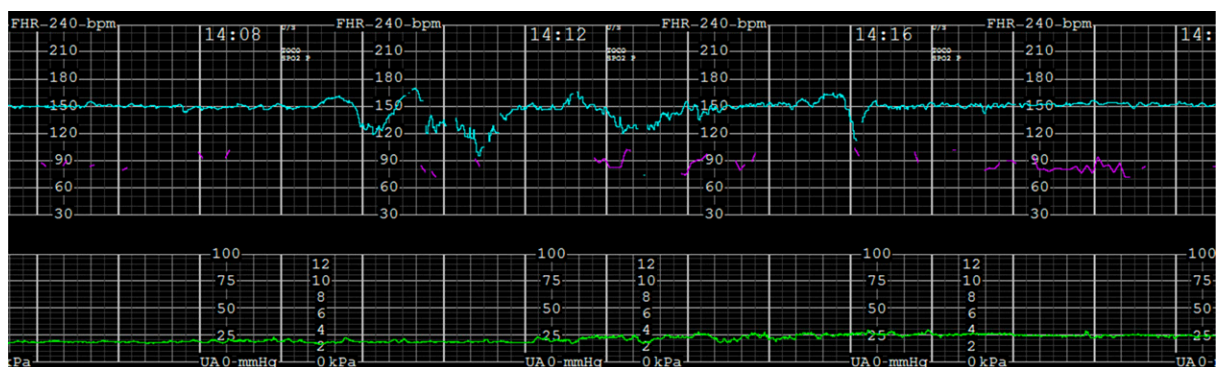


Figure 3. Electronic fetal monitoring strip 3: tracing during antepartum evaluation on hospital day 24.

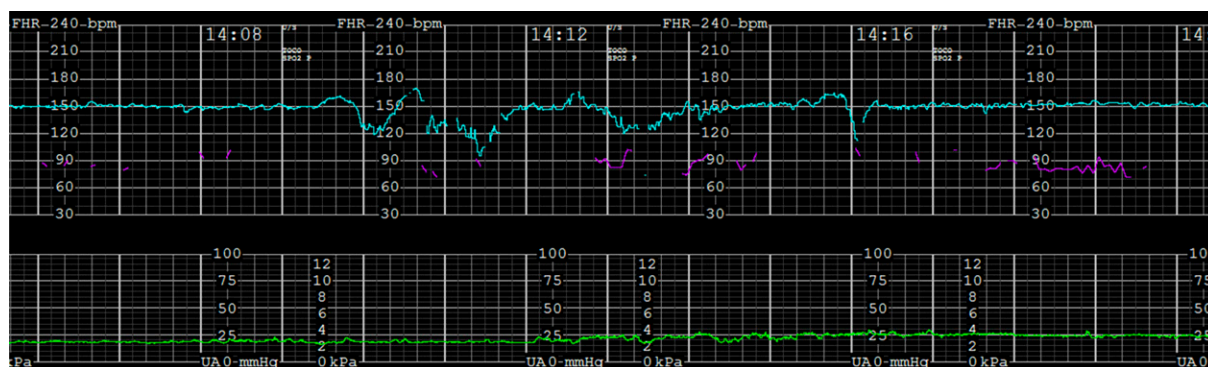


Figure 3. Electronic fetal monitoring strip 3: tracing during antepartum evaluation on hospital day 24.

Findings in EFM strip 3 are as follows (Fig 3).

- Variability: Minimal to moderate.
- Baseline: 150 beats/min.
- Episodic pattern: Recurrent variable decelerations lasting 30 seconds to 1 minute each, with return to baseline.
- Uterine contractions: None.
- Interpretation: Category II tracing.
- Differential diagnosis: Cord prolapse, cord compression, placental abruption.

- Action: Repositioning.

She was started on treatment with  $\text{MgSO}_4$  for fetal neuroprophylaxis, ampicillin for GBS positivity, and 1 dose of betamethasone as a rescue. The FHR tracing revealed a prolonged deceleration and the patient continued to have active bright red bleeding (Fig 4). Cervical evaluation was performed without evidence of cord prolapse. A cesarean section was recommended to the patient in the setting of recurrent fetal decelerations and remote from delivery.

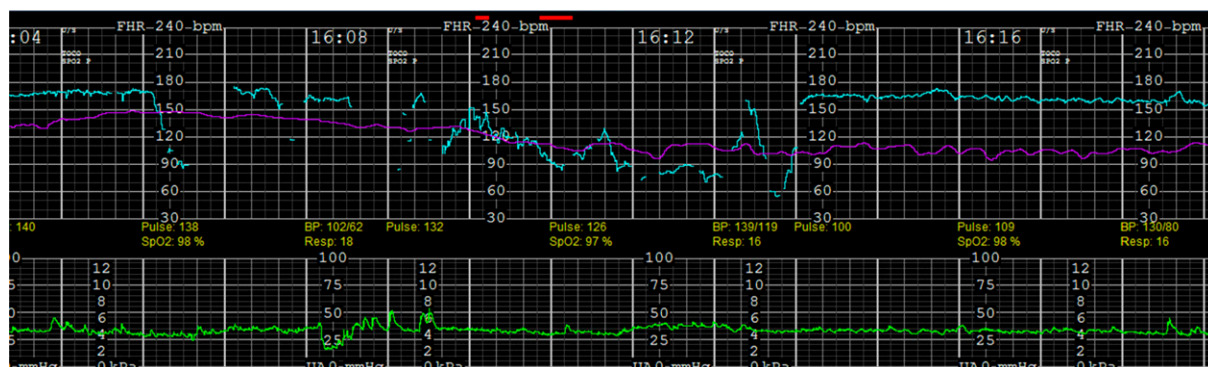


Figure 4. Electronic fetal monitoring strip 4: tracing during evaluation in the labor and delivery department on hospital day 24.

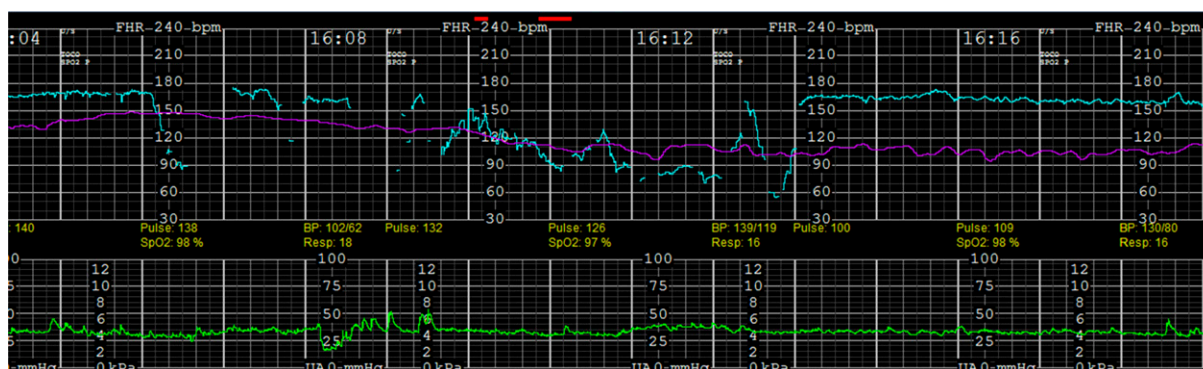


Figure 4. Electronic fetal monitoring strip 4: tracing during evaluation in the labor and delivery department on hospital day 24.

Findings in EFM strip 4 are as follows (Fig 4).

- Variability: Moderate.
- Baseline: 165 beats/min.
- Episodic pattern: 5-minute prolonged deceleration with nadir at 60 beats/min with moderate variability throughout deceleration and recovery to baseline with moderate variability. Patient bled another ~100 mL after being moved to L&D.
- Uterine contractions: None.
- Interpretation: Category II tracing.
- Differential diagnosis: Cord prolapse, cord compression, uteroplacental insufficiency, placental abruption.
- Action: Repositioning, oxygen, fluids, cervical evaluation for cord prolapse, and proceed with cesarean delivery with concern for fetal well-being.

## OUTCOME

The patient had an uncomplicated primary cesarean section and delivered a vigorous male infant at 30 weeks and 6 days of gestation. The infant emerged active and had an Apgar score of 7 and 8 at 1 and 5 minutes, respectively. The

infant's birthweight was 1,260 g (19th percentile). The umbilical arterial cord gas showed a normal pH with a normal base excess but low  $PO_2$  (Table 2). The placenta had dark maroon adherent retroplacental clot. Placental pathology included signs of maternal vascular malperfusion with placenta hypoplasia, villous infarct (subacute to remote), and accelerated villous maturation. The basal plate had focal adherent myometrial fibers and marginal insertion of the umbilical cord. There were no signs of infection. The patient had a spinal headache that resolved with a blood patch by anesthesia. She had an otherwise unremarkable recovery and was discharged on postoperative day 4 with her infant doing well in the NICU.

## DISCUSSION

PPROM is rarely associated with cessation of fluid leakage. If this does occur, the sealing of membranes is associated with a more favorable prognosis. (1) However, the patient in the current case subsequently had repeated leakage of fluid and rupture of membranes 9 weeks after her initial PPRM.

PPROM before 34 weeks' gestation is commonly managed expectantly. Therapies to improve outcome include

TABLE 2. The Patient's Arterial Cord Gas Measurements Relative to Normal and Abnormal Values

SAMPLE	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal	>7.20 (7.15–7.38)	<60	≥20	≤−10
Respiratory acidosis	<7.20	>60	Variable	≤−10
Metabolic acidosis	<7.20	<60	Variable	<−10
Mixed acidosis	<7.20	>60	Variable	≥−10
Patient	7.26	65.0	1.0	−1.8

betamethasone for fetal lung maturity, antibiotics to prolong latency, and  $\text{MgSO}_4$  to reduce the risk of cerebral palsy (before 32 weeks' gestation). (2) PPROM is associated with an increased risk of both fetal and neonatal morbidity and mortality, as well as maternal morbidity. The primary concern is prematurity. However, additional fetal and neonatal complications include infection, cord prolapse, cord compression, placental abruption, and fetal death. Placental abruption occurs in 2% to 5% of pregnancies complicated by PPROM. (3)(4)(5) The risk is increased 7- to 9-fold in PPROM pregnancies complicated by intrauterine infection or oligohydramnios. (3)(4)(5)

Labor is commonly induced in pregnancies with PPROM at 34 weeks of gestation in the absence of spontaneous labor or presence of complications that would prompt delivery. Complications that would require prompt delivery include chorioamnionitis, placental abruption, cord prolapse, or abnormal FHR tracing.

In this case, the patient began having moderate vaginal bleeding and the diagnosis of placental abruption was considered. Although the diagnosis of placental abruption does not exclude vaginal delivery, the decision for cesarean section can be made for fetal or maternal well-being. (6) Prolonged FHR monitoring of this patient showed that her fetus had recurrent variable decelerations and prolonged decelerations. Cord prolapse was assessed and not identified. The clinical diagnosis was PPROM with oligohydramnios, placental abruption, and cord compression with non-reassuring FHR tracing remote from delivery; this resulted in a decision to proceed with urgent delivery via cesarean section.

The maternal and fetal course had been stable until hospital day 24 before acutely changing. This case illustrates

the need for aggressive inpatient surveillance for PPROM that is managed expectantly as changes may occur acutely.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the causes, complications, and management of preterm premature rupture of membranes.

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# Strip of the Month: Preterm Premature Rupture of Membranes with Recurrent Variable Decelerations

Nguyen Nguyen and Scott MacGregor

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**Strip of the Month: Preterm Premature Rupture of Membranes with Recurrent Variable Decelerations**

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## A Neonate with Facial Asymmetry

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### THE CASE

A term female newborn with antenatal concern for right-sided multicystic dysplastic kidney (Fig 1) is noted to have **facial asymmetry and left microtia** (Figs 2 and 3).

### Prenatal and Birth Histories

- Born to a 21-year-old, gravida 2, para 1 woman with no significant medical history and a prior healthy child.
- Prenatal maternal laboratory findings: Normal, including an integrated sequential screen at 11 weeks' gestation.
- Prenatal ultrasonography: A routine 20-week ultrasound scan was remarkable for an enlarged right kidney and inability to visualize the stomach. A 22-week ultrasound scan demonstrated multiple cystic structures within the right renal fossa and a small cystic structure superior to the right kidney (Fig 1), and failure to visualize the fetal stomach. At 28 weeks, a small stomach was identified on ultrasonography, and a left-sided superior vena cava (SVC) was visualized on fetal echocardiography. The renal findings were consistent with right-sided multicystic dysplastic kidney disease, which, along with a small stomach and left-sided SVC, were suggestive of **VACTERL association** (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula [TEF], renal anomalies, limb abnormalities). (1) A diagnosis of TEF was also entertained because of the reduced stomach size.
- Amniocentesis performed at 22 weeks' gestation showed a normal karyotype and microarray.
- Estimated gestational age: 38 weeks.
- Spontaneous vaginal delivery.
- Apgar scores: 8 at 1 minute and 9 at 5 minutes.

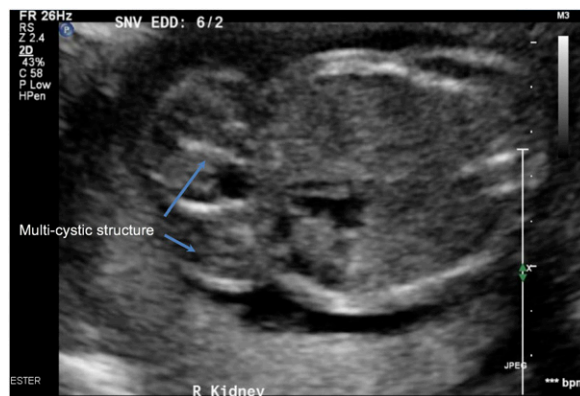


Figure 1. Ultrasound scan at 22 weeks' gestation showing right-sided multicystic dysplastic kidney.

**AUTHOR DISCLOSURES** Drs Setty and Parikh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 2. Left facial asymmetry.

### Presentation (Day 1)

The patient was transferred to the NICU shortly after delivery for further evaluation because of prenatal concern for multiple congenital anomalies.

## PROGRESSION

### Vital Signs (Day 1)

- Heart rate: 175 beats/min.
- Respiratory rate: 40 breaths/min.
- Blood pressure: 71/39 (mean 51) mm Hg.
- Oxygen saturation: 99% (in room air).
- Temperature: 98.8°F (37.1°C).

### Physical Examination (Day 1)

- Birthweight: 2.844 kg (22nd percentile).
- Length: 48 cm (28th percentile).
- Head circumference: 33 cm (26th percentile).



Figure 3. Deformed left ear with micrognathia.

- Head: Normocephalic, flat soft fontanelles, facial asymmetry with left-sided hypoplasia, mild micrognathia with left mandibular hypoplasia, left microtia with a nonpatent auditory canal, right ear had normal morphology and a patent auditory canal (Figs 2 and 3).
- Oral cavity: Pink mucosae, intact hard palate, tongue asymmetry with left-sided hypoplasia and ankyloglossia.
- Lungs: Clear, equal breath sounds bilaterally, no work of breathing.
- Cardiovascular: Regular rate and rhythm, normal S<sub>1</sub> and S<sub>2</sub>, no murmur.
- Abdomen: Nondistended, soft, no organomegaly, bowel sounds present.
- Genitourinary: Normal term female external genitalia, externally patent anus.
- Skeletal: Straight spine, no sacral cleft or dimple.
- Skin: Pink, no rashes.
- Neurologic: Normal suck and grasp reflexes, normal tone globally.

### Laboratory Studies (Day 5)

- Thyroid-stimulating hormone: 241  $\mu$ IU/mL.
- Free thyroxine (T<sub>4</sub>): 1.0 ng/dL (12.8 pmol/L).

### Radiographic Studies

- Renal ultrasonography confirmed a right multicystic dysplastic kidney (Fig 4).
- Echocardiography demonstrated a small ventricular septal defect, left aortic arch with common brachiocephalic trunk, persistent ductus arteriosus, and left SVC with dilated coronary sinus.
- Radiography did not demonstrate any vertebral abnormalities.

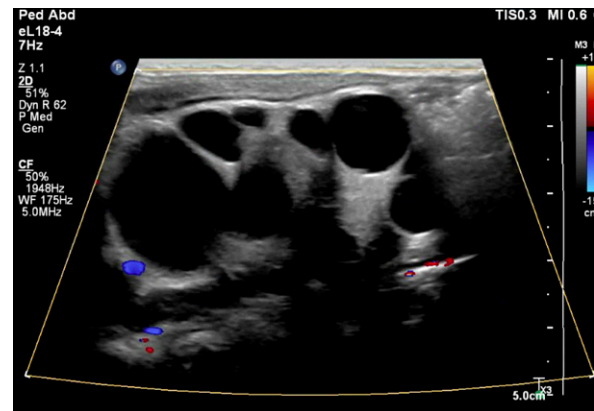


Figure 4. Postnatal ultrasound scan showing right multicystic dysplastic kidney.

- Given concern for midline defects, cranial ultrasonography was performed, which did not demonstrate any abnormalities.

A thorough evaluation was initiated to confirm the diagnosis. An eye examination demonstrated a small, raised white mass in the limbal area of the left cornea. A dilated ophthalmoscopic examination confirmed a left corneal limbal dermoid without any other abnormalities. A feeding tube was able to be passed to the stomach, ruling out esophageal atresia, though TEF was still of concern. A brainstem auditory evoked response test demonstrated **right ear conductive hearing loss** with inability to assess the left ear because of its deformation. Initial newborn screening revealed an elevated thyroid-stimulating hormone concentration; thyroid function studies confirmed the diagnosis of congenital hypothyroidism. Endocrinology was consulted and recommended thyroid ultrasonography to evaluate for **hypothyroidism** before initiating treatment. Ultrasound scans could not be obtained because of the limited capabilities of the radiology department, and hormone replacement therapy was initiated.

## DIFFERENTIAL DIAGNOSIS

Facial asymmetry with left-sided hypoplasia and ear, cardiac, and renal anomalies in a term infant:

- Branchio-oto-renal syndrome
- CHARGE (coloboma, heart defects, atresia choanae, growth restriction, genital abnormalities, and ear abnormalities) syndrome
- Goldenhar syndrome
- Nager syndrome
- VACTERL association

## Actual Diagnosis

The patient's major anomalies of a **limbal dermoid**, **mandibular hypoplasia**, and **otic deformity** led to a diagnosis of **Goldenhar syndrome**.

After the diagnosis of Goldenhar syndrome was made, the patient was transferred from the delivery hospital NICU to the nearby children's hospital for care coordination by the craniofacial team. Speech therapists worked closely with the patient on oral feeding skills. Outpatient appointments were scheduled to follow up with multiple subspecialists, including otolaryngology, cardiology, nephrology, ophthalmology, genetics, speech therapy, endocrinology, craniofacial medicine, and audiology. She was discharged from the hospital with a nasogastric tube for feeding and thyroid hormone replacement therapy. Because of aspiration on a barium

swallow study at 12 weeks of age, she underwent gastrostomy tube placement at age 6 months.

## WHAT THE EXPERTS SAY

Goldenhar syndrome falls within the **oculo-auriculo-vertebral spectrum (OAVS)**, under the broader category of craniofacial microsomias. Goldenhar syndrome is noted as **the most severe form** of OAVS, with oculo-auriculo-vertebral disorder as the mildest form and hemifacial microsomia as an intermediate form. (2)

The incidence of OAVS is thought to range from 1 in 3,500 live births to 1 in 25,000 live births. OAVS affects male patients more than female patients (ratio of 3:2). OAVS is thought to occur sporadically; some cases have been reported with an autosomal dominant inheritance pattern, and less frequently, an autosomal recessive inheritance pattern. (3) A possible pathogenic mechanism of this syndrome may be an **abnormal vascular event** in early pregnancy, which leads to **abnormal development of the first and second pharyngeal arches**, which are responsible for the growth of craniofacial structures. This syndrome has been associated with maternal exposure to retinoic acid, primidone, and thalidomide, and maternal conditions such as gestational diabetes.

The classic findings associated with OAVS include ocular, otic, and craniofacial anomalies. OAVS cases can be readily apparent at birth and characterized by a wide spectrum of signs and symptoms that can vary greatly in severity and presentation. The spectrum of malformations with OAVS can involve multiple organ systems, including central nervous, pulmonary, cardiovascular, renal, and gastrointestinal (Table). Craniofacial anomalies are usually unilateral (~60%) and cause facial asymmetry. (3) In such cases, the right side tends to be more severely affected than the left. In about 10% to 33% of OAVS cases, craniofacial anomalies can be bilateral, though one side tends to have more prominent abnormalities than the other. (2) Hypothyroidism has been reported rarely with OAVS, which was the case with this neonate. The thyroid gland forms from the branchial arches, thus **thyroid agenesis** and subsequent hypothyroidism can be features of OAVS. (4)

A prenatal diagnosis of OAVS is difficult because vertebral, gastrointestinal, and renal anomalies can be seen in numerous other conditions. For example, among the possible diagnoses for the patient, Nager syndrome and VACTERL association were thought to be less likely given a lack of extremity deformity. (1)(5) Also, CHARGE syndrome and VACTERL association were excluded, given the lack of anal and genital anomalies. (1)(5) Therefore, a thorough

TABLE. **Abnormalities in Oculo-Auriculo-Vertebral Spectrum (2)(5)**

<b>Craniofacial abnormalities</b>
Facial asymmetry
Hemifacial microsomia
Abnormal teeth development
Hypoplasia of mandible and/or maxilla
Cleft lip/palate
<b>Ocular abnormalities</b>
Epibular dermoid
Microphthalmia/anophthalmia
Coloboma
Lacrimal duct stenosis
<b>Auricular abnormalities</b>
Anotia
Microtia
Ear dysplasia with or without hearing loss
Preauricular appendages
<b>Skeletal abnormalities</b>
Vertebral defects
Extremities anomalies
<b>Cardiovascular abnormalities</b>
Atrial and ventral septal defects
Conotruncal defects
Transposition of the great vessels
Persistent truncus arteriosus
Aortic arch anomalies
<b>Gastrointestinal anomalies</b>
Tracheoesophageal atresia
Rectal atresia
<b>Central nervous system anomalies</b>
Facial palsy
Trigeminal anesthesia
Encephalocele
Microcephaly
Holoprosencephaly

Continued

TABLE. (Continued)

**Urogenital anomalies**

Multicystic kidneys
Ectopic kidneys
Renal agenesis

postnatal clinical evaluation and identification of characteristic findings is essential for early diagnosis of OAVS. Initial assessment includes a thorough physical examination followed by organ-specific evaluation, including echocardiography, renal and cranial ultrasonography, and audiology evaluation. Overall, multiple specialties are involved in the care of patients with Goldenhar syndrome, both in the hospital and as outpatients.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features and know how to diagnose craniofacial anomalies.
- Recognize the diagnostic implications of single vs. multiple anomalies.
- Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER association and DiGeorge syndrome).
- Know the laboratory features and approach to therapy of congenital hypothyroidism.

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## A Neonate with Facial Asymmetry

Shubha Setty and Pratik Parikh

*NeoReviews* 2019;20:e608

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## Intrauterine Fetal Transfusion

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### QUESTIONS

1. A woman is pregnant at 31 weeks' gestation with Rh (D)–negative, antibody-negative blood type. She develops a placental abruption, prompting delivery of a viable preterm infant with Rh (D)–positive blood type. Which of the following is recommended after delivery to prevent D-alloimmunization in the mother?
  - A. Administration of Kell immune globulin at the time of delivery will prevent Rh (D) alloimmunization.
  - B. Administration of Rho (D) immune globulin within 3 days will prevent Rh (D) alloimmunization.
  - C. Maternal treatment is only needed if the infant's blood type is Rh (D) negative.
  - D. There is no treatment available to prevent Rh (D) alloimmunization.
2. Unfortunately she does not receive the appropriate treatment. She then has a miscarriage while traveling and has an extremely elevated anti-D antibody titer in her next pregnancy 2 years later. She is diagnosed with fetal anemia at 22 weeks' gestation and ultimately has a procedure (Video 1). What procedure is being shown in this video?
  - A. Fetal umbilical vein transfusion
  - B. Intraperitoneal transfusion
  - C. Rho (D) immune globulin administration
  - D. Termination of pregnancy because of expected severe outcome



Video 1. Fetal intraperitoneal transfusion.

**AUTHOR DISCLOSURES** Drs Teodoro, Sudhof, and Shinker have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## DISCUSSION

Alloimmunization is the development of antibodies to foreign red blood cell antigens. Fetal red blood cell antigens are determined by maternal and paternal red blood cell phenotypes. If the fetus expresses antigens foreign to the pregnant woman, the woman can develop immunoglobulin G (IgG) antibodies to this foreign antigen that can then cross the placenta to the fetus. This can occur in cases of fetomaternal hemorrhage, when there is mixing of fetal and maternal blood. Fetomaternal hemorrhage is associated with obstetric events, such as delivery—including miscarriage—and abdominal trauma; however, fetomaternal hemorrhage can also occur in the antenatal period and often goes undiagnosed unless it results in poor fetal testing, stillbirth, or neonatal anemia. (1) The transplacental transfer of maternal IgG antibodies to the fetus can lead to fetal isoimmunization, anemia, hydrops, and death. (2)

Although many different blood group antibodies exist, the most common is the Rhesus (Rh) group, which includes D, E, and C alleles. (3) D antigen incompatibility is the most common cause of severe hemolytic disease in the fetus. Preventing Rh (D) antigen alloimmunization with administration of Rho (D) immune globulin (ideally within 3 days of fetal blood exposure) has sharply decreased rates of anti-D alloimmunization; however, this intervention cannot be used to treat patients who have already been sensitized to D or who have alloimmunization against other blood antigens. (2)(4) Other than Rho (D) immune globulin, there are no immune globulins commercially available for any of the other red blood cell antigens. Other less common but clinically significant antibodies include Kell, Rh group E and C, Duffy, MNS, P, and ABO. (4)(5)

When a pregnant woman is diagnosed with positive blood group antibodies, she needs to be counseled about options for assessing fetal risk for hemolytic disease. Prenatal diagnosis by amniocentesis is the most direct way to assess fetal blood antigens. Another option is to determine the paternal blood phenotype (if known and accessible) and then decide whether to proceed with amniocentesis based on whether the father is heterozygous or homozygous for the antigen. Cell-free DNA testing can be used to screen for an Rh (D)-positive fetus; although this is currently used in Europe, it is not the standard of care in the United States because of concern for false-negative results.

Fetuses that are deemed to be at risk for hemolytic disease are screened for anemia. It has been determined that anemic fetuses have faster blood flow through the middle cerebral artery (MCA) than those without anemia.



Video 2. Fetal umbilical vein transfusion.

This difference likely represents a compensatory response of increased cerebral blood flow in the fetus in the setting of fetal anemia. The increased peak systolic velocity can be detected noninvasively with MCA velocity Doppler assessment. (6) MCA Doppler should be performed on a weekly basis in fetuses at risk for isoimmunization once the antibody of concern has reached a critical titer (specific to local laboratory thresholds) at a gestational age when intervention would be feasible, usually after 22 weeks. When the MCA peak systolic velocity is greater than 1.5 multiples of the median for gestational age, percutaneous umbilical blood sampling and intrauterine transfusion of the fetus can be performed to confirm and correct fetal anemia, respectively. Blood can be administered to the fetus directly via the umbilical vein or into the fetal abdominal cavity as an intraperitoneal transfusion. Video 1 shows intraperitoneal transfusion, with “ascites” representing the blood transfused thus far. The swirling of blood can be seen in the video as the fetus is receiving the transfusion. Video 2 shows an intrauterine transfusion through the umbilical vein, with

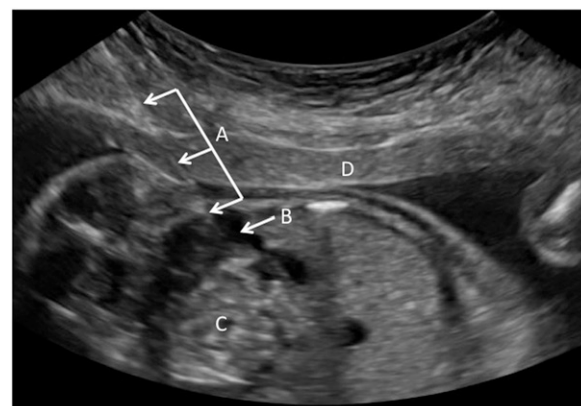
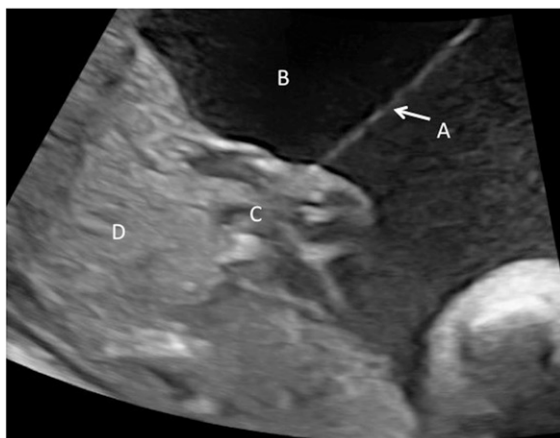


Figure 1. Intrauterine transfusion for the fetus with anemia. A=needle; B=intraperitoneal transfused blood; C=fetal bowel; D=uterine wall.



**Figure 2.** Percutaneous umbilical blood sampling and intrauterine transfusion for the fetus with anemia. A=needle; B=amniotic fluid; C=placental cord insertion; D=placenta.

blood swirling along the course of the umbilical cord. The relevant fetal structures are labeled in Figs 1 and 2.

Early antibody screening, primary prevention, and intravascular transfusion have almost eliminated alloimmune-mediated fetal hydrops. (7) Compared with intraperitoneal transfusion, fetal umbilical vein transfusion results in significantly better clinical outcomes for both the pregnant woman and the fetus, and thus intraperitoneal transfusion is reserved for situations in which transfusion into the umbilical vein is technically not feasible. (8) This is usually the case when the transfusion is performed early in gestation or the placental cord insertion is not easily accessible. Later in gestation (after 34 weeks), the risks of the procedure have to be weighed against the risks of premature delivery of a severely anemic fetus; thus, consultation with both neonatology and maternal-fetal medicine is recommended.

## CORRECT RESPONSES

1. Answer: B. Administration of Rho (D) immune globulin within 3 days will prevent Rh (D) alloimmunization. In the current case, determining neonatal blood type will determine the need for Rho (D) immune globulin. If the neonate is Rh (D) negative, the risk of D alloimmunization is zero. If the neonate is Rh (D) positive, Rho (D) immune globulin should be administered in a timely fashion. If there is concern for fetomaternal hemorrhage, then testing maternal blood for the amount of fetal cells will help ensure that

the mother receives the adequate dose of Rho (D) immune globulin.

2. Answer: B. Intraperitoneal transfusion.

Intrauterine transfusion, performed intraperitoneally (as shown in Video 1) or directly into the umbilical vein, will optimize outcomes for this pregnancy. Now that she is alloimmunized, this patient is not a candidate for Rho (D) immune globulin. Each subsequent pregnancy with an Rh (D)-positive fetus will have worsening severity of hemolytic disease of the fetus. Before 32 to 34 weeks' gestation, fetal transfusion is preferred over delivery.

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- Know the diagnostic evaluation and perinatal management of fetal-maternal blood group incompatibility.

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## Berry Brazelton: Le Magnifique

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I was privileged to have worked with Berry Brazelton (Fig) for over 40 years. In 1978, as a new graduate student from Ireland, I first looked over his shoulder in the company of his pediatric fellows, as he used the scale he had just developed—the Neonatal Behavioral Assessment Scale (NBAS)—to examine a less than 1-day-old female newborn in the old Boston Lying-In Hospital. Even as he examined the baby's reflexes, I was immediately struck by his—what could only be called gentleness, even tenderness—in the way he both held and spoke to the baby. He called her by her first name. “You are so alert, Sarah. Your mother must be very proud of you.” When he took a red ball out of his kit and moved it slowly from 1 side to the other, the baby began to track the ball and locked on to it, as if she did not want to release it from her gaze. “She can see,” blurted her mother, shaking her head in disbelief. When he began to talk to her in lilting, melodic phrases, Sarah's face relaxed and her eyes widened and brightened. They were now interacting with each other—in a give-and-take, back-and-forth cyclical rhythm that had all the hallmarks of true conversation.

That babies could see and hear and had a wide repertoire of behavioral endowments at birth was a revelation to me, but Berry Brazelton had just demonstrated that this less than 1-day-old baby also had her own well-defined personalized behavioral style and was already shaping and leaving her mark on the world. She and Berry Brazelton left their mark on me and on all the pediatric fellows who were present on that August day, many years ago.

In this clinical newborn encounter, we can see 3 principles that can be said to characterize Berry Brazelton's enduring legacy: firstly, the recognition of newborns as competent and social beings, ready to engage and interact with their environments from the very beginning. Secondly, by integrating parents into the pediatric session he demonstrated the effectiveness of the newborn examination as a teaching tool, on the one hand, and the newborn period as a powerful intervention “touchpoint,” on the other. He maintained that pediatricians, neonatologists, nurses, and allied perinatal health care professionals are in a unique position to make a significant contribution to the lives of parents and children, at this particularly vulnerable time in the parent's lives. The third principle or stance embraced by Dr Brazelton on that day highlighted the importance of listening to parents and the need for clinicians to be able to translate and communicate with parents in a way that is nonjudgmental, culturally sensitive, and jargon-free. Indeed, it was this capacity to translate theory and research into accessible language without diminishing its complexity or soft-peddling its urgency that made him so popular with parents and made him a household name in North America and beyond. It also made him a powerfully effective advocate for health care reform and a champion of parents' rights.

Berry Brazelton died in March 2018 at age 99. For more than 70 years, he advised parents and health care professionals from almost every discipline—and even counseled presidents—about child rearing and child development. He may

**AUTHOR DISCLOSURE** Dr Nugent has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure. Berry Brazelton (courtesy of Insieme photo by Fulvia Farassino).

not have been the first pediatrician to realize that newborn babies were more competent than had been acknowledged, but he played a central, if not *the* central, role in changing conventional perceptions of the newborn among health care professionals and parents alike around the world. Even among scientists, the dominant view for much of the 20th century was that the newborn infant was essentially a “blank slate” at birth, endowed with so-called primitive motor reflexes, which required no cortical involvement and thus, was only capable of spontaneous reflexive behavior in response to stimulation. Brazelton’s innovative work with newborns opened the door to a whole generation of clinicians, researchers, and parents and made it possible for them to discover and personalize the human newborn. Indeed, he was one of the earliest figures in medicine to build a bridge between the sometimes-arcane world of clinical practice and the general public. The appeal of his work was that complex ideas were expressed with brilliant simplicity—he had the rare gifts of a great teacher and communicator.

### “GOOD WITH BABIES”

“Berry is good with babies,” his grandmother remarked. She encouraged him to become a pediatrician because she recognized his precocious capacity to “connect” with babies

and young children, even when he was a very young boy. In his 2013 memoir, *Learning to Listen: A Life Caring for Children*, he wrote, “I could keep them amused and safe and keep them from crying for up to two hours at a time.” Encouraged by his grandmother (née Berry, a descendant of the Duc de Berry), Berry Brazelton saw pediatrics as a vocation, as a calling to dedicate his life to serving the health needs of children and their families. Like the Duc de Berry—*le magnifique de France*—the medieval French knight, who dominated much of France in the 14th century, Berry Brazelton also was an explorer—searching, pursuing, questioning, relentlessly looking for novel solutions in new lands. Indeed, he traversed the globe, studying children’s development and examining child-rearing practices, from the highlands of Chiapas in Mexico to Kenya, where he studied Gusii child-rearing practices, to the southern United States, where he worked with Navajo leaders, and on to the Goto Islands where he worked with Japanese colleagues in a longitudinal study of child development. This experience in diverse environments of child development enabled him to explore questions of universality and cultural variation in mothers’ and children’s behavior and in terms of his own practice, made him open to differences in belief and practice wherever he encountered them.

### THE NEWBORN EXAMINATION

Brazelton went to Columbia University Medical School and afterwards completed his medical residency at the Massachusetts General Hospital in Boston and then, as if on script, chose pediatric training at Boston Children’s Hospital. But when he first began to work in the newborn nursery, he was struck not just by the limitations of the existing pediatric examination in capturing the full richness of the baby’s behavioral repertoire but also by the negative or deficit-based thrust of these scales. Up to then, the newborn was assumed to be merely operating at a brainstem level. The newborn assessment tools used by most pediatricians at that time reflected these assumptions, so that even the more sophisticated neonatal scales, such as those by Andre-Thomas and Saint-Anne Dargassies (1960) and Amiel-Tison (1968), in France, focused exclusively on the assessment of the so-called “primitive reflexes” and “postural reactions” to identify various disorders.

To redress this, Brazelton began his quest to develop a more comprehensive assessment tool, one that could do justice to the baby’s capacities and more importantly, from his point of view, a newborn scale that could capture the individuality of each baby. This spurred him on to seek out and then join Jerome Bruner—arguably one of the great

minds of the 20th century—at the Center for Cognitive Studies at Harvard University, in an effort to integrate developmental theory and neurological principles into his clinical understanding of newborn behavior and development. Observing babies and toddlers in this unique laboratory setting confirmed his growing conviction that every child was different and that each child needed a different kind of care and support, all of which challenged the maturational “milestone” or “one-size-fits-all” approach to child development which informed pediatric guidance at that time.

### “COURTEOUS TO BABIES”

Given his interest in individual differences in children, not surprisingly, perhaps, Brazelton’s first research study focused on infant crying. The study included a sample of 80 mothers of healthy full-term newborn infants, whom he asked to keep daily records of their infants’ fussing for the first 12 weeks of age. He reported that while there was an average of 2½ hours daily crying in the first 7 weeks, there was a wide range in individual differences in the amount and rate of crying behavior across this period (Brazelton, 1962). Not long after, he presented his ideas on individual differences to a wider audience in his groundbreaking book, *Infants and Mothers: Differences in Development*, the first sentence of which reads, “Normal babies are not all alike.” In this best-selling book, he presented a contrast between the development of the very active, the moderately active, and the quiet baby, which led Bruner to remark in the preface that, “Dr Brazelton has an unflagging sense of human individuality....he invites us to be courteous to the infants, who are our children and he helps us achieve this courtesy by sketching the range of individual expression that infancy can take.”

### A NEW RESEARCH TRADITION

Fortunately for Brazelton, in addition to Jerome Bruner, a new generation of researchers at this time, stimulated by the work of Jean Piaget and Erik Erikson, and including Colwyn Trevarthen, Jerome Kagan, Daniel Stem, Ken Kaye, Lewis Lipsitt, Arnold Sameroff, Heidelise Als, Ed Tronick, Barry Lester, and others, had begun to develop novel ways to study learning in infancy in an effort to determine how early and under what conditions infants could learn. This new body of research provided Brazelton with a rich empirical database for subsequent conceptualizations of newborn and infant development. Although it had been assumed that the newborn could see only shadows at birth, Robert Fantz

demonstrated that as early as 18 hours after birth, not only can babies see but they prefer to look at complex rather than simple patterns. He also went on to show that babies preferred to look at a human face than at any other pattern (Fantz, 1961). It was also believed that babies could not hear because their ears were filled with fluid at birth, but in the same year, Michael Wertheimer’s research showed that before they were 10 minutes old, neonates were able to turn in the direction of an auditory stimulus (Wertheimer, 1961).

Then, Peter Wolff, based on a study of 22 infants who were observed in their homes for 30 hours each week during the first months after birth, showed that newborns had distinctly organized behavioral states—deep sleep, light sleep, quiet alert, active alert, and crying states. He went on to examine how state transitions and changes can influence developmental transformations in the infant’s social-emotional behavior and development (Wolff, 1959). These data provided the evidence Brazelton needed to show that the newborn infant was, indeed, competent and complexly organized.

### THE DEVELOPMENT OF THE NBAS

Stimulated by this body of research, the first iteration of the NBAS appeared, known as the Cambridge Behavioral and Neurological Scales, which Brazelton developed along with psychologist Daniel Freedman from the University of Chicago and which he now used to test the applicability of the concept of individual differences (Brazelton & Freedman, 1971). One of the first studies with this scale provided evidence for clearcut behavioral differences between Chinese-American neonates and American babies of Northern European origin (Freedman and Freedman, 1969). In the same year, Brazelton went to Mexico to test out the new scale in a study of the behavior of Zinacanteco Indians in the highlands of Chiapas. The behavior of the Zinacanteco neonates was strikingly different from white infants in North America, according to Brazelton, and he and his colleagues reported that they had a more uniform quiet activity level, allowing for long periods of responsiveness to auditory and visual signals, and the caregiving practices of the Zinacanteco mothers seemed to reinforce this quiet sustained alertness (Brazelton et al, 1969). This cross-cultural experience, coupled with his own systematic observations of infant cry patterns, prompted him to continue his quest for an assessment scale that could describe the full range of individual and cultural differences in newborn behavior.

Brazelton did not reach his rich understanding of the capabilities of newborn infants overnight or alone. Many scholars contributed to his understanding of the newborn infant, while he, in turn, enriched their understanding of early parent-child relationships with his rare appreciation of the sensibilities and vulnerabilities of new parents. With help from Daniel Freedman, Frances Degan Horowitz, Barbara Koslowski, John Robey, Henry Riciutti, Arnold Sameroff, and Edward Tronick, Brazelton produced the first edition of the NBAS, published in 1973. He graciously invited me to be the coauthor of the NBAS on the subsequent editions.

However, at that time, the doors of academic publishing houses in the United States were closed to this new scale, undoubtedly deterred by its novel unorthodox character, which included items measuring the infant's visual and auditory capacities when it was universally assumed that babies could neither see nor hear at birth! This new assessment scale may have included classic neurological items such as the Glabella reflex and the Moro response, but it also included items that measured the infant's "cuddliness" and "attractiveness," which were deemed to defy objective measurement. But Berry Brazelton did not relent. Finally, he had to cross the Atlantic where he met Ronald McKeith and Martin Bax at the Spastics Society Medical Education and Information Unit in London, who hailed this new assessment as one that would revolutionize the field and predicted that it "would be used for many years to come." They agreed to publish the NBAS in 1973, and within a few years, it was hailed as the most comprehensive examination of newborn behavior available and was increasingly used in research studies across the globe.

## RESEARCH WITH THE NBAS

Never conceptualized as an objective assessment in the classic psychometric or medical diagnostic tradition, with an emphasis on pass/fail criteria, the NBAS is based on a broader appreciation of the complexity of newborn behavior, including the newborn's motor and social interactive capacities. The scale consists of 28 behavioral items, which measure the infant's behavioral capacities, and 16 reflex items, which measure the infant's neurological status (Brazelton, 1973, 1984, Brazelton and Nugent, 1995, 2011). Because it is sensitive to even subtle environmental effects, the NBAS has demonstrated that newborn behavior and development can be affected by many variables including intrauterine growth restriction, low birthweight, and prematurity (Costas et al, 1989; Figueras et al, 2011; Lester et al, 1986); environmental polychlorinated biphenyls (Sagiv et al, 2006); different modes of delivery and obstetric medication

(Lester et al, 1982; Sepkoski et al, 1992); neonatal hyperbilirubinemia (deCaceres et al, 1991); maternal ingestion of toxins such as cocaine, tobacco, alcohol, and caffeine (Mansi et al, 2007; Morrow et al, 2001; Nugent et al, 1991; Tronick, 1987); and predicting later atypical development or developmental delay and disability (Bedford et al, 2015; Ohgi et al, 2002; Shoaff et al, 2018) (See Brazelton & Nugent [2011], for a detailed review of NBAS studies). In addition, a large number of studies have used the NBAS in different cultural settings (Nugent et al, 1989, 1991). This body of research reveals a wide range of variability in newborn behavioral differences across cultures and suggests that whereas the basic organizational processes in infancy may be universal, the range and form of these adaptations are shaped by the demands of each individual culture. In this way, cross-cultural studies using the NBAS have expanded our understanding of the range of variability in newborn behavior patterns and the diversity of child-rearing practices and belief systems across settings (Nugent, 1995; Nugent et al, 2009).

The NBAS can be said to have played a major role in expanding the understanding of the phenomenology of newborn behavior among researchers and clinicians alike and has, in turn, stimulated the development of a number of scales for use with different populations and in different settings. Als and colleagues, for example, used the concepts of the NBAS to develop the Assessment of Preterm Infants' Behavior, an assessment of the behavior of the preterm infant (Als et al, 1989), while Lester and Tronick used the NBAS as the basis for the Neonatal Intensive Care Unit Network Neurobehavioral Assessment Scale (Lester and Tronick, 2004). Keefer (1995) developed the combined Physical and Behavioral Neonatal Examination, while Cardone and Gilkerson (1995) also used the concepts of the NBAS to develop the Family Administered Neonatal Activities.

The Newborn Behavioral Observations (NBO) system also comes from this tradition and was developed by Nugent et al as a relationship-building instrument, designed to sensitize parents to the capacities and individuality of the newborn infant and to foster the relationship between parent and infant and between clinician and family (Nugent et al, 2007). A series of studies have shown that the NBO is an effective tool for perinatal professionals to enable parents to build positive relationships with their newborns (McManus & Nugent, 2012; Nugent et al, 2014; 2017).

## ADVOCATING FOR PARENTS

Although Berry Brazelton's work with the NBAS reflected a deep appreciation of and respect for the baby



as a unique individual, he maintained an equally respectful stance toward parents. Almost from the outset, Brazelton realized that the pathological, deficit-based thrust of his medical training left him ill-prepared for meeting the needs of the parents who came to his office with concerns about their baby's behavior, such as sleep, crying, or toilet-training issues. Moreover, the "mother-blaming" thrust of existing approaches to child guidance ran counter to his natural sympathetic stance toward parents and his awareness of how much energy, passion, and wisdom parents bring to the task of parenting. While he advocated for parents, he helped physicians and patients understand each other better, broke down the barriers among physicians, patients, and the public at large, and encouraged parents to look within themselves for answers to their parenting challenges. He proposed that the newborn period and the first months of age presented perinatal professionals with a unique opportunity to support parents in this quest, by offering them unconditional respect and nonjudgmental support.

## THE TRAINING OF PROFESSIONALS IN CHILD DEVELOPMENT

Hand in hand with his work with newborns and their families, Brazelton turned his attention to pediatric training, where he saw the need to provide training designed to increase pediatricians' awareness of young children's behavior. He firmly believed that perinatal professionals were in a uniquely privileged position to support parents at a time when parents often felt alone and vulnerable. Combining his interests in primary care pediatrics and child psychiatry, he set up one of the first training programs for pediatricians at the Child Development Unit and went on to play a pivotal role in the establishment of Behavioral and Developmental Pediatrics as a pediatric subspecialty. He believed that pediatricians needed to be schooled in developmental and infant mental health theories and in a more strength-based, family-centered approach to pediatric care.

In an oral history interview at the American Academy of Pediatrics, he said that pediatricians should be able to offer parents help and resources to deal with behavioral issues and concluded that "We're very good at identifying everything that's wrong with anybody, but we don't have any idea about what's going on in them or what's right about them" (<https://www.aap.org/en-us/about-the-aap/Gartner-Pediatric-History-Center/DocLib/Brazelton.pdf>).

## ACTIVISM AND ADVOCACY

Brazelton came to believe that programs and policies that serve children are most effective when they are informed by data and evidence and grounded in deep knowledge of child development and rely on cutting-edge research, independent analyses, actionable recommendations, and clear communications to improve policies and interventions that serve children and their families. He was an evidence-based optimist, animated by a utopian purpose and frequently appeared before congressional committees, playing a key role in the enactment of the Family and Medical Leave Act, which guarantees 3 months of maternity leave, and Public Law 99-457, which extends the rights and protections of the Individuals with Disabilities and Education Act to young children. He also served on the National Commission on Children. His resolve, combined with his sympathetic sensibilities, transformed him into an activist pediatrician. He saw health issues not just as individual problems but also as a consequence of social justice, which involves providing better health and social care services for currently underserved populations with unmet needs.

## THE DANCE OF IDEAS

The poet Rilke, wrote, "*Be patient toward all that is unsolved in your heart and try to love the questions themselves.*" Berry Brazelton knew that science begins by asking questions and then seeking answers. He fostered curiosity, a sense of wonder, a thirst for knowledge, a need to know more. When, as a newly arrived student, I first entered the meeting room in the 3-story Victorian building which housed the Child Development Unit at Boston Children's Hospital, I watched him lead a discussion on the genes-environment debate, surrounded by 10 or so of his fellows. I half-sat on the chair feeling unworthy to be in this august academic setting.

But, despite the give-and-take first name-laden informality and the palpable camaraderie, the discussion was impassioned and opinionated. Clearly, this was no conventional lecture and was unlike anything I had ever experienced, so that when Dr Brazelton turned to me and asked me on which side I was in the genes-versus-environment debate, I surprised myself by offering an opinion. But the answer was not important. It was the fact that he had honored me by asking that struck me so powerfully on that day and that Berry Brazelton assumed I had something to contribute. In that stunning revelatory moment, I knew that that this was a place where one could learn.

Brazelton mastered the art of asking good questions. Adopting the Socratic method, he simply posed the kinds of

questions that led the conversant to further question his or her own beliefs. He knew that a good open-ended question can excite, disturb, or comfort, and eventually yield an unexpected bounty of understanding and critical awareness. His ease in asking questions and his humility in learning from others is a mark of his greatness. This was the reason he had a reserve of apparently intuitive supernatural gifts, which allowed his mind to roam and, on occasion, enigmatically reveal some of its secrets hidden from ordinary mortal view. We were often dazzled by his instant understanding of the deeper dynamics of every case and by his imaginative interventions, but his genius lay in his curiosity and his ability to ask questions. He was never afraid to say, “I don’t understand. What do you mean?” This humility led to the dance of ideas.

## RESOLVE, HUMILITY, AND HOPE

While Berry Brazelton will be remembered by many of our generation for his warm fixed photogenic *carpe diem* smile, suggesting an easygoing fun-loving disposition, beneath this smile was a leonine resolve and determination; indeed it may well have been that steely mindset that led to the sheer range and breadth of his achievements across a lifetime. He remained a stubborn researcher, an engaged clinician, and an inveterate advocate for parents and families throughout his life, so that for today’s generation of young pediatricians and neonatologists, his life offers inspiration and hope.

He was a powerfully effective advocate for health care reform and, as a champion of parents’ rights, he was outstanding. If one might find a hidden emotional spine to all his work, it is that policies that support families are critical, as the strength and quality of the relationship between caregivers and their children are fundamental to the effective development of children’s brain functions and capacity. While the backdrop to Berry Brazelton’s monumental achievements in the field seems to have been a rare combination of energy, charisma, warmth, persistence, determination and zest, more than all else, it included an ease in asking questions and humility in learning from others—a true humility that is the mark of greatness.

I will end this tribute with a quote from the great Nobel Prize-winning Irish poet, William Butler Yeats:

*Think where man’s glory most begins and ends  
And say my glory was I had such friends.*

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## Historical Perspectives: Berry Brazelton: Le Magnifique

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# Update on Erythropoiesis-Stimulating Agents Administered to Neonates for Neuroprotection

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## Education Gaps

This review summarizes multiple preclinical and clinical trials to evaluate the use of erythropoiesis-stimulating agents (ESAs) to improve neurodevelopmental outcomes. Multiple proposed mechanisms of action by which ESAs improve neuronal health are discussed, and trials involving preterm and term patient populations are reviewed. Together, this information provides evidence that ESAs have the potential to improve neurodevelopmental outcomes in infants.

## Abstract

Erythropoiesis-stimulating agents (ESAs) such as erythropoietin and darbepoetin have been studied as red blood cell growth factors in preterm and term infants for more than 30 years. Recently, studies have focused on the potential neuroprotective effects of ESAs. In this review, we summarize preclinical animal models and recent clinical trials that provide evidence for ESAs as potential treatments to improve neurodevelopmental outcomes in preterm and term infants.

## Objectives After completing this article, readers should be able to:

1. Explain the mechanisms of action by which erythropoiesis-stimulating agents (ESAs) may provide neuroprotective properties.
2. Be familiar with clinical trials investigating the use of ESAs in the preterm population in relation to neurodevelopment.
3. Describe the use of ESAs in term infants and specific conditions in which ESAs may promote improved neurodevelopmental outcomes.

## ERYTHROPOIESIS-STIMULATING AGENTS: ERYTHROPOIETIN AND DARBEPOETIN

Early studies of red blood cell production identified a substance that stimulated erythropoiesis. In 1971, Goldwasser and Kung (1) purified erythropoietin (Epo)

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## ABBREVIATIONS

BSID	Bayley Scales of Infant Development
CI	confidence interval
Darbe	darbepoetin
ELBW	extremely low birthweight
Epo	erythropoietin
Epo-R	erythropoietin receptor
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FSIQ	full-scale IQ
HAWIK-III	Hamburg-Wechsler-Intelligenztests für Kinder-III
HIE	hypoxic-ischemic encephalopathy
HIF	hypoxia-inducible factor
IL	interleukin
IV	intravenous
IVH	intraventricular hemorrhage
JAK2	Janus tyrosine kinase 2
MDI	Mental Developmental Index
MRI	magnetic resonance imaging
ROP	retinopathy of prematurity
SC	subcutaneous
STAT	signal transducer and activator of transcription
TH	therapeutic hypothermia
TUNEL	terminal deoxynucleotidyl transferase dUPT nick end labeling



from the plasma of anemic sheep, but it was not until 1985 that the gene for Epo was cloned by Lin and colleagues. (2) Amgen Pharmaceuticals was the first company to produce human recombinant Epo, which they named Epogen. The US Food and Drug Administration (FDA) approved Epogen soon thereafter (in 1989) for use in adults with chronic kidney disease.

Continued work by Amgen investigators involved evaluation of a variety of modified molecules to increase the half-life of Epo. Darbepoetin (Darbe, trade name: Aranesp) was bioengineered by Amgen in 2001 using recombinant DNA technology to create hyperglycosylated recombinant human Epo analogues. (3) The additional carbohydrate chains increased the serum half-life 3-fold and provided greater in vivo activity, allowing for less frequent administration. Epo and Darbe, termed erythropoiesis-stimulating agents (ESAs), have been studied for more than 30 years in a variety of patient populations. In this review, we summarize recent preclinical and clinical studies in neonates evaluating potential neuroprotective and neuroreparative properties of ESAs.

## Epo NEUROPHYSIOLOGY

In the nervous system, neuronal progenitor cells, endothelial cells, mature neurons, and glial cells all express Epo receptors (Epo-Rs). (4) Although Epo is able to cross the blood-brain barrier through Epo-R expressed on brain capillaries, (5) it is also produced in the brain, (6) primarily by astrocytes, and is noted to be slightly smaller in size compared with Epo produced in the kidneys. (7) The expression of Epo in the brain is primarily regulated by hypoxia-inducible factor (HIF)-1, which becomes activated in response to stressors, including hypoxia, hypoglycemia, and oxidative stress. (8) Preclinical studies determined that Epo plays an important role in normal neurodevelopment, as a lack of Epo-R results in a reduction of neural progenitor cells and increased apoptosis. (9) In humans, it has been observed that Epo and Epo-R are present in the brain during embryogenesis as early as 5 weeks after conception. (10)

The role of Epo and Epo-R in the brain, including mechanisms of action, continues to be investigated. Mechanisms for neuroprotective properties of Epo include decreased inflammation, decreased apoptosis, decreased oxidant injury, increased neurogenesis, and increased angiogenesis. (11) A discussion of these proposed mechanisms by which Epo results in neuroprotection follows.

### Anti-inflammatory Mechanisms

Although the exact mechanisms of the anti-inflammatory properties of Epo are not known, studies have shown

reductions in proinflammatory cytokines and an increase in anti-inflammatory cytokines after treatment with Epo. Specifically, in an animal model of traumatic brain injury, suppression of the proinflammatory cytokines interleukin (IL)-1 $\beta$  and tumor necrosis factor  $\alpha$  and an increase in the anti-inflammatory cytokine IL-10 occurred after treatment with Epo. (12) Investigators evaluating an animal model of subarachnoid hemorrhage reported that treatment with Epo reduced mRNA expression of tumor necrosis factor  $\alpha$  and IL-1 $\beta$  and increased expression of the anti-inflammatory cytokines IL-4 and IL-10. (13) It is unclear whether the anti-inflammatory properties of Epo are the result of direct cytokine action or rather secondary to decreased neuronal apoptosis. Other preclinical models of Epo administration have shown similar increases in anti-inflammatory cytokine expression and decreases in proinflammatory cytokine expression, (14)(15)(16) resulting in an overall anti-inflammatory effect of Epo.

Influencing macrophage polarization is another mechanism by which Epo may have anti-inflammatory properties. In a mouse model of diabetes, there was an increased number of macrophages with an M2 phenotype (preferential release of anti-inflammatory cytokines) over an M1 phenotype (preferential release of pro-inflammatory cytokines) after treatment with Epo. (17) The Janus tyrosine kinase 2 (JAK2)/signal transducer and activator of transcription (STAT) pathway is involved in macrophage polarization. Both JAK2 and STAT3 expression were increased after Epo treatment, with a resultant decrease in M1 phenotype macrophages observed. (17) This pathway was also altered after Epo treatment in a model of subarachnoid hemorrhage. The JAK2/STAT3 pathway was activated after Epo treatment, resulting in microglial polarization to the M2 phenotype over the M1 phenotype. (13) Thus, Epo may impact cytokine expression by altering microglial polarization into the phenotype with preferential release of anti-inflammatory cytokines.

### Antiapoptotic Mechanisms

The primary mechanism by which Epo is thought to enhance neuronal health is through antiapoptosis. Epo treatment has resulted in a decrease in the number of terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive neurons after a reversible 60-minute middle coronary artery occlusion in rats. (8) This same model has also shown an approximately 75% reduction in the infarct volume after Epo treatment. (8) Brain-derived neurotrophic factor is released primarily from astrocytes and acts to enhance neuronal survival, neurogenesis, and neurite outgrowth. (18) Brain-derived neurotrophic factor is

released from astrocytes, which then affects the Epo and sonic hedgehog pathways, resulting in neuroinflammatory regulation. (18) A meta-analysis of 18 publications reported a significant decrease in the size of an infarct by 30% after treatment with Epo in animal models of stroke. (19) In addition, Epo administration results in decreased apoptosis in cortical neurons and hippocampal neurons. (20) The action of Epo binding to its receptor results in activation of the JAK2 pathway, which then leads to phosphorylation of additional downstream signaling pathways, including phosphatidylinositol 3-kinase/protein kinase B, resulting in cell survival and prevention of neuronal apoptosis. (21)

### Antioxidant Properties

Oxidative stress is a mechanism through which neuronal injury may occur. The recombinant form of Epo has been shown to scavenge different radicals, including hydroxyl, 2,2-diphenyl-1-picrylhydrazyl and peroxy, thus acting as a biological antioxidant. (22) HIF (which induces Epo production) also protects against apoptosis after oxidative stress. (20) A preclinical model revealed an increase in astroglial glutathione peroxidase production after Epo administration, which augmented the antioxidant defense system. (23) In addition, a murine study revealed that Epo treatment suppressed reactive oxidative species in cultured microglia, providing supportive evidence for the antioxidant properties that Epo may have in the central nervous system. (24) Differential effects were observed in astrocytes and microglia in the latter study, indicating that protective properties of Epo may be cell-type specific. This potential protective mechanism requires further investigation. Administration of recombinant Epo in 20 preterm infants born at less than 33 weeks' gestation resulted in significantly decreased ferritin concentrations and serum malondialdehyde levels, indicating a significant decrease in lipid peroxidation. (25) The authors hypothesized that the decrease was secondary to inhibition of iron-catalyzed free radical reactions.

### Neurogenesis Promotion

Epo has been shown to increase neuronal development by binding to Epo-R on oligodendrocytes and immature neuronal precursors. (26)(27) Injury during development results in an upregulation of Epo-R, (20)(26) presenting a unique opportunity for potential administration of exogenous Epo. Preclinical studies have observed enhanced neurogenesis after Epo administration in a rat model of stroke. Likewise, administration of anti-Epo neutralizing antibody resulted in inhibition of neurogenesis, (28) suggesting autocrine or paracrine activity. (7) After prenatal systemic hypoxic-ischemic brain injury in a preclinical rat model, Epo administration resulted

in improved oligodendroglial lineage cell genesis and survival, (29) supporting the hypothesis that Epo was effective in promotion of neurogenesis. In addition, activation of the phosphatidylinositol 3-kinase/protein kinase B pathway when Epo binds to its receptor also activates matrix metalloproteinases 2 and 9, which can promote neurogenesis through enhanced neural progenitor cell migration. (21) Epo promotes the development of neuronal stem cells into astrocytes, which have previously been shown to induce neurogenesis. (30)

### Angiogenesis Promotion

Epo production is induced by hypoxia via activation of the transcription factor family HIF. The latter process also regulates vascular endothelial growth factor. (20) A mouse model of permanent focal cerebral ischemia showed enhanced angiogenic activity with Epo treatment, with upregulation of the expression of angiogenic factors Tie-2, angiopoietin-2, and vascular endothelial growth factor. (31) In addition, a decrease in the number of TUNEL- and caspase-3-positive endothelial cells was observed after Epo treatment, indicating neurovascular protection. (31) Preclinical models have also demonstrated revascularization of the ischemic zone in the brain after hypoxic injury, resulting in improved oxygenation of the tissues. (32)

Epo and Epo-R are present in the fetus during development. Epo is present in amniotic fluid. It has been proposed that increased amniotic fluid Epo levels occur in the setting of fetal hypoxia, with fetal plasma Epo levels correlating with amniotic fluid Epo levels. (33) A model of asphyxia in preterm sheep showed reduced neuronal loss after Epo treatment, a significant reduction in the number of seizures and the total seizure burden, and increased neuronal survival on histopathologic analysis in the striatal caudate nucleus, CA3, and dentate gyrus of the hippocampus and thalamic medial nucleus. (34) In addition, Epo treatment resulted in a greater total number of oligodendrocytes and a reduction in the number of activated caspase-3-positive cells in the white matter tracts. (34)

### Opportunity for Intervention

The preclinical literature investigating the impact of Epo on the developing brain is quite promising, with multiple proposed mechanisms by which Epo may improve neuronal health. However, the exact timing of Epo administration, the dose to use, and the type of prenatal/perinatal injury that is most responsive to treatment continue to be explored.

## CLINICAL STUDIES OF ESA NEUROPROTECTION

Several investigators have evaluated neuroprotective and neuroregenerative properties of ESAs in adult patients with

a variety of disease processes, including stroke, Alzheimer disease, Parkinson disease, traumatic brain injury, spinal injury, and psychiatric diseases (such as schizophrenia and depression). (35)(36) The administration of ESAs for neonatal neuroprotection focuses primarily on 2 populations: preterm infants and term infants with hypoxic-ischemic encephalopathy (HIE).

### Clinical Studies in Preterm Infants

Carnielli and colleagues (37) were the first investigators to administer Epo to preterm infants in 1989. European (38) and US (39) multicenter studies followed, in which lower (based on adult pharmacokinetics) doses of Epo were used to stimulate red blood cell production and decrease transfusion requirements. Pharmacokinetic analyses (40)(41) (42) confirmed significant differences between adults and neonates in Epo clearance and volume of distribution such that higher doses were required in preterm infants. Studies evaluating appropriate Epo doses in preterm infants resulted in decreased transfusions and decreased donor exposures.

As the potential for neuroprotection of ESAs was being investigated in preclinical studies, the neurodevelopmental outcomes of former preterm infants previously enrolled in clinical trials of ESAs originally designed to decrease transfusions were reexamined. Neubauer and colleagues (43) evaluated 148 children at 10 to 13 years of age who as preterm infants had been randomized to receive Epo or placebo (control) in various multicenter Epo studies (Table 1). Children who received Epo during their initial NICU stay scored significantly better than untreated children in overall developmental assessment (55% [Epo] vs 39% [controls] were normally developed;  $P < .05$ ) as well as in measures of cognition (mean composite Hamburg-Wechsler-Intelligenztests für Kinder-III [HAWIK-III] IQ score, 90.8 [Epo] vs 81.3 [controls];  $P < .005$ ). The greatest difference was found in children who had brain injury due to intraventricular hemorrhage (IVH): those who were randomized to receive Epo scored significantly better than placebo-treated children with IVH (52% vs 6% developed normally; composite HAWIK-III IQ score, 90.3 vs 67.0;  $P < .005$ ). Based on these observations, Epo seemed to be a potential treatment for extremely low birthweight (ELBW; birthweight  $< 1,000$  g) infants, particularly for those with brain injury as a result of IVH.

Bierer and colleagues (44) were the first to publish observations regarding an association between cognitive scores at 2 years and circulating Epo concentrations (Table 1). A post hoc analysis of ELBW infants enrolled in the National Institute of Child Health and Human Development Neonatal Research

Network Epo study (51)(52) reported significantly higher Bayley Scales of Infant Development (BSID) II Mental Developmental Index (MDI) scores in infants with peak serum Epo concentrations greater than 500 mU/mL. These findings led to the design of further studies specifically evaluating the potential of ESAs to improve neurodevelopmental outcomes.

Developmental outcome data (45) were collected at 12 to 36 months' corrected gestational age on available individuals originally enrolled in the high-dose Epo study in ELBW infants performed by Juul and colleagues. (53) Thirty infants in the original Epo-treated cohort received a total of 3 doses of intravenous (IV) Epo (500, 1,000, or 2,500 U/kg). The untreated and Epo-treated infants had similar birth characteristics and postnatal growth. Analysis of neurodevelopmental follow-up scores from Epo-treated infants (17 of 25 infants originally enrolled) and control infants (18 of 26 originally enrolled) showed that Epo-treated infants had better BSID-II scores.

Our group completed follow-up of infants enrolled in a randomized, masked placebo-controlled trial of ESAs administered to very low birthweight infants (birthweight  $< 1,500$  g) enrolled from 2006 to 2010 (NCT00334737). (46) A total of 99 infants were randomized to receive subcutaneous (SC) Darbe (10  $\mu$ g/kg once per week), Epo (400 U/kg 3 times per week), or placebo through 35 weeks' postconceptual age. Of the 99 infants evaluated during the hospital phase of the study, 94 survived to discharge, and 80 (29 Epo, 27 Darbe, 24 placebo) returned for follow-up at 18 to 22 months of age. Mean  $\pm$  SD BSID-III cognitive scores were significantly higher in Darbe ( $96.2 \pm 7.3$ ) and Epo ( $97.9 \pm 14.3$ ) recipients compared with placebo recipients ( $88.7 \pm 13.5$ ;  $P = .01$  versus ESA recipients) by an analysis of covariance with adjustment for sex. (46) In addition, Darbe and Epo recipients had a significantly higher test score for object permanence compared with placebo recipients ( $P = .05$ ), providing the first published evidence of improved early executive function. (46) No infants in the ESA groups had cerebral palsy compared with 5 in the placebo group ( $P < .001$ ). There were no differences in either visual or hearing impairment; overall neurodevelopmental impairment was significantly less in the ESA groups compared with the placebo group (odds ratio, 0.18; 95% confidence interval [CI], 0.05–0.63). In addition to providing evidence of improved executive function in former preterm infants receiving ESAs, this was the first study to report improved cognitive outcomes in preterm infants receiving Darbe.

Infants enrolled in the ESA trial summarized previously herein were eligible for long-term follow-up in a National Institute of Child Health and Human Development–funded study, the Brain Imaging and Developmental Follow-up of

**TABLE 1. Clinical Studies of ESAs and Neuroprotection in Preterm Infants**

SOURCE	PARTICIPANTS	ESA DOSING	OUTCOMES
Neubauer et al, 2010 (43)	171 Former ELBW infants previously enrolled in multiple RCTs, evaluated at age 10–13 y: 89 Epo treated, 57 placebo controls	250 U/kg IV or SC Epo 3×/wk in first 2 wk (77 infants) or after 2 weeks (12 infants); placebo controls	55% of Epo-treated children developed normally (IQ > 84, no neurodevelopmental deficits), 39% of controls developed normally, $P < .05$ ; HAWIK-III IQ 90.8 vs 81.3, $P < .001$ Epo-treated children with IVH scored significantly better than untreated children (52% vs 6% normally developed; composite HAWIK-III IQ score, 90.3 vs 67.0; $P < .02$ )
Bierer et al, 2006 (44)	15 ELBW infants: 7 Epo treated, 8 placebo treated	400 U/kg IV or SC Epo 3×/wk from birth through 35 weeks' PMA; placebo	Epo: BSID-II MDI, $96 \pm 11$ ; PDI, $87 \pm 13$ ; NDI in 2 of 6 survivors Placebo: BSID II MDI, $78 \pm 7$ ; PDI, $80 \pm 7$ ; NDI in 4 of 6 survivors MDI scores in infants with peak serum Epo concentrations $\geq 500$ mU/mL were greater than those in infants with concentrations $< 500$ mU/mL ( $100 \pm 15$ vs $77 \pm 16$ ; $P < .05$ )
McAdams et al, 2013 (45)	60 ELBW infants: 30 Epo treated, 30 controls	500, 1,000, or 2,500 U/kg IV Epo $\times$ 3 doses	17 of 25 Epo-treated and 18 of 26 control infants identified that Epo correlated with improvement of BSID-II MDI ( $R = 0.22$ , $P = .044$ ) and PDI ( $R = 0.15$ , $P = .026$ )
Ohls et al, 2014 (46)	99 Preterm infants with 500–1,250 g birthweight: 33 Epo treated, 33 darbepoetin treated, 33 placebo treated	400 U/kg SC Epo 3×/wk; 10 $\mu$ g/kg SC darbepoetin once a week; placebo; all infants treated through 35 weeks' PMA	BSID-III composite cognitive scores higher in darbepoetin ( $96.2 \pm 7.3$ ) and Epo ( $97.9 \pm 14.3$ ) recipients compared with placebo recipients ( $88.7 \pm 13.5$ ; $P = .01$ vs ESA recipients); object permanence scores higher in ESA group ( $P = .05$ ). No ESA recipients had cerebral palsy compared with 5 in the placebo group ( $P < .001$ ).
Ohls et al, 2016 (47)	53 Children previously treated with ESAs or placebo as preterm infants; 24 control children previously born term	Treated during initial hospitalization: 400 U/kg SC Epo 3×/wk; 10 $\mu$ g/kg SC darbepoetin once a week; placebo; all infants treated through 35 weeks' PMA	Children randomized to receive ESAs, (39) placebo, (14) and term controls. (24) FSIQ and PIQ were significantly higher in the ESA group compared with the placebo group (FSIQ: $91.1 \pm 17.5$ vs $79.2 \pm 18.5$ , $P = .036$ ; PIQ: $93.0 \pm 17.0$ vs $79.5 \pm 19.5$ , $P = .018$ ); children receiving ESAs performed better than placebo on executive function tasks.
Natalucci et al, 2016 (48)	448 Preterm infants 26–32 weeks' gestation, no grade 3 or 4 IVH; 228 Epo treated, 220 placebo treated	3,000 U/kg IV Epo, given at 3, 12–18, and 36–42 h of age for a total of 3 doses	BSID-II MDI: Epo group, $93.5 \pm 16.0$ (95% CI, 91.2–95.8); placebo group, $94.5 \pm 17.8$ (95% CI, 90.8–98.5) (difference, $-1.0$ [95% CI, $-4.5$ to $2.5$ ]; $P = .56$ ); no differences in secondary outcomes
Song et al, 2016 (49)	800 Preterm infants 26–32 weeks' gestation, no grade 3 or 4 IVH; 366 Epo treated, 377 placebo treated	500 U/kg IV Epo, given every other day for 2 wk	Death or moderate/severe neurologic disability occurred in 91 of 338 infants (26.9%) in the placebo group and in 43 of 330 infants (13.0%) in the Epo group (RR = 0.40, 95% CI, 0.27–0.59; $P < .001$ )

*Continued*

TABLE 1. (Continued)

SOURCE	PARTICIPANTS	ESA DOSING	OUTCOMES
Mayock et al, 2019 (50)	942 ELGANS 24–28 weeks' gestation; 432 Epo treated, 424 placebo treated	1,000 U/kg IV Epo every other day for 6 doses; 400 U/kg SC Epo 3×/wk through 32 completed weeks' gestation	26% of Epo-treated and 26% placebo-treated infants had death or severe disability (RR = 1.03; 95% CI, 0.81–1.32); death or severe disability was lower in Epo-treated 27-week gestation infants (RR = 0.47; 95% CI, 0.23–0.94; <i>P</i> = .02)
Darbepoetin 2020	650 ELGANS 23–29 weeks' gestation	10 µg/kg IV or SC darbepoetin once a week through 35 completed weeks' gestation	Primary outcome: No differences in morbidities between groups; final analyses being completed Enrollment nearly complete

BSID=Bayley Scales of Infant Development, CI, confidence interval, ELBW=extremely low birthweight; ELGANS=extremely low gestational age neonate, Epo=erythropoietin, ESA=erythropoiesis-stimulating agent, FSIQ=full-scale IQ, HAWIK-III=Hamburg-Wechsler-Intelligenztests für Kinder-III, IV=intravenous, IVH=intraventricular hemorrhage, MDI=Mental Developmental Index, NDI=neurodevelopmental impairment, PDI=Psychomotor Developmental Index, PIQ=performance IQ, PMA=postmenstrual age, RCT=randomized controlled trial, RR=relative risk, SC=subcutaneous.

Infants Treated with ESAs (BRITE) Study. Fifty-four former preterm infants randomly assigned to receive Darbe, Epo, or placebo through 35 weeks' postconceptual age were evaluated at 2 time points: 3.5 to 4 years of age (4 years) (47) and 5.5 to 6 years of age (6 years). (46) The control group consisted of 24 healthy children who had delivered full term. The full-scale IQ (FSIQ) and general language from the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, were used with all participants to obtain an overall measure of executive function on the basis of tests evaluating inhibitory control and spatial working memory. Infants in the ESA group (*n* = 39) had significantly higher mean  $\pm$  SD FSIQ and performance IQ scores compared with the placebo group (*n* = 14) (FSIQ score:  $91.1 \pm 17.5$  vs  $79.2 \pm 18.5$ , *P* = .036; performance IQ score:  $93.0 \pm 17.0$  vs  $79.5 \pm 19.5$ , *P* = .018). In addition, children who had received ESAs performed better on executive function tasks compared with children who had received placebo. The ESA group's performance was below that of term controls (*n* = 24) at 4 years, but by 6 years the ESA and term groups were similar on both cognitive and executive function tasks. The ESA-treated group had better cognitive outcomes and less developmental impairment at 4 and 6 years of age compared with the placebo group, thus supporting the results that neurodevelopmental impairment was greater in the children who had received placebo compared with the children who had received ESAs. These long-term results support ongoing evaluation of ESAs as potential neuroprotective treatments to improve long-term cognitive outcomes of infants born prematurely.

A high-dose Epo study was performed from 2005 to 2012 by Fauchere and colleagues in Switzerland (NCT00413946).

(54) Investigators randomized 448 preterm infants (26–32 weeks' gestation; infants with preexisting grade 3 or 4 IVH were excluded) during the first 3 hours after birth to receive IV Epo (3,000 U/kg bodyweight) or placebo at 3, 12 to 18, and 36 to 42 hours after birth. The primary outcome of the study was BSID-II MDI measured at 24 months' corrected age. There were no differences in common preterm morbidities, including IVH or retinopathy of prematurity (ROP), during hospitalization. Of 448 preterm infants randomized (mean gestational age, 29.0 weeks; mean birthweight, 1,210 g; 59% female), 228 were randomized to receive Epo and 220 placebo, with outcome data available for 365 infants (81%) at a mean age of 23.6 months. There was no significant difference in the neurodevelopmental outcome between the 2 groups, with the mean  $\pm$  SD MDI being  $93.5 \pm 16.0$  (95% CI, 91.2–95.8) in the Epo group and  $94.5 \pm 17.8$  (95% CI, 90.8–98.5) in the placebo group (difference,  $-1.0$  [95% CI,  $-4.5$  to  $2.5$ ]; *P* = .56), as well as no differences in the secondary outcomes. (48) In addition, subgroup analyses of neuroimaging in these infants at term-equivalent age revealed improved outcomes in Epo-treated patients. (55)(56)

Although the results of the Swiss study were not significant, a similar patient population was evaluated by Song and colleagues from 2009 to 2013. (49) These investigators administered Epo for neuroprotection at lower doses (500 U/kg every other day  $\times$  2 weeks) in a preterm population (26–32 weeks' gestation; infants with grade 3 or 4 IVH before randomization were excluded). A total of 800 infants were randomly assigned to receive IV Epo, 500 U/kg every other day for 2 weeks (*n* = 366), or placebo (*n* = 377) within 72 hours after birth. Neurodevelopmental outcome data



were available for 668 infants (83.5%). The primary outcome of death or moderate/severe neurologic disability was significantly different between groups at 18 months' corrected age: only 43 of 330 infants (13.0%) in the Epo group compared with 91 of 338 infants (26.9%) in the placebo group (relative risk, 0.40; 95% CI, 0.27–0.59;  $P < .001$ ) had death or moderate/severe neurologic disability. Assessing for the rate of moderate/severe neurologic disability only revealed a significant improvement in the infants receiving Epo (22 of 309 infants [7.1%]) compared with the infants receiving placebo (57 of 304 infants [18.8%]; relative risk, 0.32; 95% CI, 0.19–0.55;  $P < .001$ ). There were no excess adverse events observed, but the infants in the Epo group did have significantly fewer blood transfusions compared with the placebo group ( $P < .001$ ). Despite excluding infants with preexisting grade 3 or 4 IVH, the incidence of intracranial hemorrhage was significantly higher than reported in a comparable population of preterm infants in NICUs throughout the United States, (57) and higher than the population studied by Fauchere and colleagues. This may explain, in part, the differences in outcomes that were found between the 2 studies.

**Retinopathy of Prematurity.** Similar to previous large randomized trials, there were no differences in the incidence of any stage of ROP (or visual impairment at 18–22 months' corrected age) in the 3 recently published multicenter trials. (46)(49)(54)(58) In addition, preliminary data from the recently completed Preterm Erythropoietin Neuroprotection Trial (PENUT; NCT01378273) reported no difference in ROP between the Epo and placebo groups. (50) A meta-analysis performed in 2006 suggested a link between Epo administration during the first week after birth and an increased risk of stage 2 ROP (59) compared with administration of Epo after the first week of age. (60) However, the data were not represented accurately because of a misclassification of 1 of the Epo centers into the late administration group. (61) With the addition of more recent studies evaluating ESA administration in preterm infants, the association between ESAs and ROP was no longer found to be significant for either early or late Epo administration. In fact, the association between the early use of ESAs and a decreased incidence of ROP is nearly significant ( $P = .07$ ). Although preterm infants enrolled in Epo clinical trials are monitored for ROP, the misperception that early Epo administration increases the risk of ROP greater than stage 2 can be laid to rest.

### Clinical Studies in Term Infants

Investigators recognized that ESAs might be ideally suited for use in neonates with neonatal encephalopathy due to

HIE in that the potential neuroprotective and neuroreparative effects mirrored biochemical mechanisms of perinatal injury. Initial studies evaluating Epo for neuroprotection in term infants with HIE were performed on infants who did not receive therapeutic hypothermia (TH) (Table 2). Zhu and colleagues (62) randomized 167 term infants with moderate or severe HIE to either conventional treatment ( $n = 84$ ) or Epo, 300 U/kg (52 infants) or 500 U/kg (31 infants) every other day for 2 weeks ( $n = 83$ ). The first dose was administered SC and subsequent doses were administered IV. In the control group, 35 of the 80 infants (44%) had moderate/severe disability or death at 18 months compared with the Epo group (25%;  $P = .017$ ). The primary outcomes were similar with both Epo doses. In infants with moderate to severe HIE, the response to Epo was comparable with the response to TH reported in previous trials (69) in that an overall 20% decrease in death or disability was identified.

Elmahdy and colleagues (63) examined biochemical and neurophysiologic parameters associated with SC Epo administration at 2,500 U/kg for 5 days (NCT00945789). Thirty infants with mild to moderate HIE were randomized to the Epo (3 mild, 12 moderate) or control (4 mild, 11 moderate) group, with 15 additional term infants included in the study as healthy controls. The serum nitric oxide levels were measured at enrollment and repeated in infants with HIE at 2 weeks of age. Additional assessments included electroencephalography at enrollment and at 2 to 3 weeks, brain magnetic resonance imaging (MRI) at 3 weeks, and a neurologic examination at 6 months. As expected, infants with HIE had elevated serum nitric oxide levels compared with healthy controls. Electroencephalography and serum nitric oxide levels showed improvement in the infants with HIE who received Epo; however, the brain MRIs showed no significant differences. Interestingly, there were functional improvements in the infants treated with Epo, with fewer neurologic and developmental abnormalities observed at the 6-month assessment compared with controls. This led the authors to conclude that the use of Epo in infants with HIE is feasible and beneficial.

Malla and colleagues (65) also evaluated Epo in term infants with HIE who were not provided TH. Investigators randomized 100 term neonates with moderate or severe HIE to receive either placebo or IV Epo 500 U/kg every other day for a total of 5 doses, with the first dose given by 6 hours of age. The primary outcome was death or moderate/severe disability at 19 months. Although both groups had a similar mortality rate (16%), the Epo group had a lower risk of moderate or severe disability (40%) compared with the placebo group (70%) (risk ratio, 0.57; 95% CI, 0.38–0.85;  $P = .003$ ). Brain abnormalities on MRI, cerebral palsy, and the use of



TABLE 2. **Clinical Studies of ESAs and Neuroprotection in Term Infants**

SOURCE	PARTICIPANTS	ESA DOSING	OUTCOMES
Zhu et al, 2009 (62)	167 infants $\geq 36$ weeks' gestation with moderate to severe HIE	300 U/kg (52 infants) or 500 U/kg (31 infants) IV Epo every other day for 2 wk; controls (84 infants)	<p>Reduced death or disability in the Epo group vs the control group (24.6% vs 43.8%; RR = 0.62; 95% CI, 0.41–0.94; <math>P = .017</math>, 38% relative reduction) at 18 mo of age.</p> <p>Outcomes were not different between the 300- and 500-U/kg doses of Epo.</p> <p>Epo improved long-term outcomes only for neonates with moderate HIE (<math>P = .001</math>) and not those with severe HIE (<math>P = .227</math>).</p>
Elmahdy et al, 2010 (63)	30 infants $\geq 36$ weeks' gestation with mild to moderate HIE	2,500 U/kg SC Epo $\times$ 5 d (15 infants); controls (15 infants)	<p>Neurodevelopmental outcomes according to the Denver Developmental Screening Test II and neurologic examinations at 6 mo of age significantly improved (<math>P = .03</math>) in the Epo group.</p> <p>Reduction in nitric oxide concentration (<math>P &lt; .001</math>) at 2 wk of age in the Epo group.</p> <p>No difference in MRI findings between the Epo and control groups.</p>
El Shimi et al, 2014 (64)	30 infants $\geq 36$ weeks' gestation with moderate to severe HIE	1,500 U/kg IV Epo $\times$ 1 (10 infants); TH alone (10 infants); supportive care (10 infants); term controls (15 infants)	<p>Survival was 60% in TH, 30% in the Epo group, 20% in the supportive care group. MRI score and neuromuscular function score were similar in the HT and Epo groups.</p>
Malla et al, 2017 (65)	100 infants $\geq 36$ weeks' gestation with moderate to severe HIE	500 U/kg IV Epo every other day for 5 doses (50 infants); controls (50 infants)	<p>Improved survival without neurologic abnormality (RR = 0.65; 95% CI, 0.45–0.94; <math>P &lt; .01</math>) in the Epo group.</p> <p>There was a 30% absolute reduction in combined outcome of death or moderate/severe disability at mean age of 19 mo in the Epo group (RR = 0.57; 95% CI, 0.38–0.85; relative reduction, 43%; <math>P &lt; .003</math>).</p> <p>Mortality rate was similar between the groups.</p> <p>There was a reduction in risk of cerebral palsy, neonates on anticonvulsant treatment at assessment, electroencephalography abnormality, and abnormal brain MRI in the Epo group.</p>
Wu et al, 2012 (66)	24 infants $\geq 36$ weeks' gestation with moderate to severe HIE undergoing TH	Dose escalation: IV Epo, 250 U/kg (3 infants), 500 U/kg (6 infants), 1,000 U/kg (7 infants), 2,500 U/kg (8 infants) every other day $\times$ 6 doses	<p>Brain MRI performed at a median of 6 d (range, 4–13 d) of age and using different protocols revealed no intracranial hemorrhages or venous thromboses.</p> <p>The MRI was normal in 13 infants (54%) and demonstrated watershed injury in 9 (42%), basal ganglia injury in 1 (4%), and focal arterial infarction in 1 (4%).</p>
Baserga et al, 2015 (67)	30 infants $\geq 36$ weeks' gestation with moderate ( $n = 20$ ) to severe ( $n = 10$ ) HIE undergoing TH	Darbepoetin, 2 $\mu$ g/kg (10 infants), 10 $\mu$ g/kg (10 infants); placebo (10 infants)	<p>Similar adverse events in the 3 groups; area under the curve was 26,555 for 2-<math>\mu</math>g/kg dose and 180,886 h*mU/mL* for 10-<math>\mu</math>g/kg dose</p>

Continued

TABLE 2. (Continued)

SOURCE	PARTICIPANTS	ESA DOSING	OUTCOMES
Wu et al, 2016 (68)	50 infants $\geq 36$ weeks' gestation with moderate to severe HIE undergoing TH	1,000 U/kg IV Epo on days 1, 2, 3, 5, and 7 (24 infants); placebo (26 infants)	<p>No difference in neonatal mortality (8% vs 19%; <math>P = .42</math>).</p> <p>Brain MRI at mean <math>\pm</math> SD of <math>5.1 \pm 2.3</math> d showed a lower global brain injury score in Epo-treated neonates (median, 2 vs 11; <math>P = .01</math>).</p> <p>Moderate/severe brain injury (4% vs 44%; <math>P = .002</math>), subcortical (30% vs 68%; <math>P = .02</math>), and cerebellar injury (0% vs 20%; <math>P = .05</math>) were less frequent in the Epo vs placebo group.</p> <p>At 12 mo of age there was significant improvement in Alberta Infant Motor Scale score (53.2 vs 42.8; adjusted treatment effect, 10.2; 95% CI, 1.9–18.5; <math>P = .03</math>) but no difference in Warner Initial Developmental Evaluation score (122 vs 110; adjusted treatment effect, 10.8; 95% CI, –2.8 to 24.5; <math>P = .15</math>).</p> <p>The composite outcome of death or moderate/severe neurodevelopmental impairment was not different between the groups (16.7% in the Epo group vs 38.5% in the placebo group; <math>P = .12</math>).</p> <p>There was a trend in reduction in severity of brain injury on MRI at 12 mo of age in the Epo group (35% vs 12%; <math>P = .09</math>).</p>

CI=confidence interval, Epo=erythropoietin, ESA=erythropoiesis-stimulating agent, HIE=hypoxic-ischemic encephalopathy, IV=intravenous, MRI=magnetic resonance imaging, RR=relative risk, SC=subcutaneous, TH=therapeutic hypothermia.

anticonvulsant agents were greater in the placebo group. The investigators concluded that Epo monotherapy reduced the risk of death or disability in term neonates with moderate or severe encephalopathy. This study demonstrated an overall decrease in death or disability similar to the results of whole-body TH trials. Nevertheless, because the current standard of care for infants with moderate to severe HIE is TH, the overall generalizability of the Epo studies is limited.

El Shimi and colleagues (64) performed a head-to-head comparison of Epo and TH and compared short-term outcomes. They enrolled 45 infants: 30 were randomized to receive supportive care (10 infants), TH (10 infants), or a single dose of SC Epo (1,500 U/kg; 10 infants) and 15 were healthy nonasphyxiated infants. Survival at 3 months of age was better in the TH group (60%) than in the single-dose Epo group (30%). MRI scores and neuromuscular function scores were similar between the TH and EPO groups.

#### TH with ESAs

To determine the safety, efficacy, and pharmacokinetics of Epo administration combined with TH, Wu and colleagues (66) enrolled 24 infants with moderate to severe HIE in an

open-label, dose escalation trial of Epo (NEAT Trial [Neonatal Erythropoietin in Asphyxiated Term Newborns], NCT00719407) (Table 2). Consent was obtained from 92% of families approached. Infants received either 250, 500, 1,000, or 2,500 U/kg IV Epo every other day for a maximum of 6 doses, and pharmacokinetic data were obtained with the first, second, and last doses. Epo followed nonlinear pharmacokinetics, with no serious adverse effects or deaths reported. Epo was noted to not accumulate with multiple dosing (the area under the curve was 50,306, 131,054, and 328,002 U $\cdot$ h/L for 500, 1,000, and 2,500 U/kg, respectively). Thus, the dosing of 1,000 U/kg of IV Epo was concluded to be well tolerated in infants receiving TH and produced plasma concentrations similar to those with observed neuroprotection in preclinical animal models.

Based on the results of their dose escalation study, Wu and colleagues (68) randomized 50 term infants with moderate to severe HIE undergoing TH to receive placebo ( $n = 26$ ) or IV Epo ( $n = 24$ ), 1,000 U/kg on days 1, 2, 3, 5, and 7. Infants were evaluated at 12 months using an infant

motor scale and a parent development questionnaire. MRI findings were independently scored by observers blinded to treatment arm. Two infants in the Epo group and 5 infants in the placebo group died. The Epo group had a lower global injury score on MRI performed at 5 days, and motor function was better at 12 months of follow-up. The authors concluded that TH plus high-dose Epo treatment resulted in less brain injury and improved motor outcomes at 1 year of age.

Investigators from Hebei Province in China evaluated 41 infants randomized to receive TH plus IV Epo, 200 U/kg per day  $\times$  10 days starting on the second hospital day ( $n = 21$  infants) compared with TH alone ( $n = 20$  infants). (70) Serum tau protein levels were compared to determine the level of neuronal injury (higher levels reflect greater neuronal injury), and developmental and behavioral assessments were performed. Compared with the control group, serum tau protein levels were lower and neonatal behavioral neurologic assessment scores were higher in the Epo group at 8 and 12 days; however, there were no differences in neurodevelopmental outcome between the 2 groups at 9 months of age. For this study, Epo was diluted in 10% dextrose water, which might have decreased the actual dose delivered, as ESAs require either protein or polysorbate 80 to remain stable in solution. (71)

Baserga and colleagues (67) studied Darbe administration in term infants with HIE who were undergoing TH (Table 2). The DANCE study (Darbepoetin Administered to Neonates Undergoing Cooling for Encephalopathy; NCT01471015) enrolled 30 infants with moderate to severe HIE. Infants were randomized to receive placebo or Darbe, 2 or 10  $\mu\text{g/kg}$  IV, administered once before 12 hours of age and again on day 7. Pharmacokinetics for the 10- $\mu\text{g/kg}$  group showed an area under the curve of 180.886  $\text{h}\cdot\text{mU/mL}$  and a terminal half-life of 53.4 hours, approximately 3 times the half-life of Epo reported in the NEAT Trial. The authors did not find any adverse effects associated with Darbe administration. Investigators speculated that Darbe might be a better choice than Epo due to its longer half-life and the fewer doses that are needed.

A recent meta-analysis evaluating investigations of ESA treatment for infants with moderate or severe HIE concluded that ESAs improved neurodevelopmental outcomes over TH alone. (72) Based on these studies, several multicenter clinical trials evaluating ESAs in conjunction with TH in term infants with HIE are in progress:

- High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL; NCT02811263)
- Erythropoietin for Hypoxic Ischemic Encephalopathy in Newborns (PAEAN; NCT03079167)

- Efficacy of Erythropoietin to Improve Survival and Neurological Outcome in Hypoxic Ischemic Encephalopathy (Neurepo; NCT01732146)
- Mild Encephalopathy in the Newborn Treated with Darbepoetin (MEND; NCT03071861)

In addition, a randomized controlled study is being performed evaluating the neuroprotective effects of Darbe in neonates with ischemic stroke (Darbepoetin for Ischemic Neonatal Stroke to Augment Regeneration (DINOSAUR; NCT03171818).

## CONCLUSION

The neuroprotective properties of ESAs, including promotion of oligodendrocyte development despite neuronal injury, are evident in animal models. Initial clinical studies of ESA administration in term and preterm infants have demonstrated promising results, as several investigations have reported improved neurodevelopmental outcomes in preterm infants as well as in term infants recovering from HIE. We believe that ESAs should continue to be evaluated as potential neuroprotectants in clinical trials to further assess their usefulness in preventing and treating brain injury in term and preterm infants.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the evolution of neurodevelopmental impairments during development and the difference between transient and permanent impairments in NICU graduates (eg, developmental delay versus intellectual disability; tone abnormalities versus cerebral palsy).
- Know the clinical features, diagnosis, and management of perinatal hypoxic-ischemic encephalopathy.
- Know the outcome of infants with hypoxic-ischemic encephalopathy.

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1. Darbepoetin is an erythropoietin (Epo) analogue that has which of the following characteristics compared with Epo?
  - A. Decreased glycosylation.
  - B. A 3-fold increased serum half-life.
  - C. Decreased in vivo activity.
  - D. Found more commonly naturally in mammalian serum.
  - E. No ability to bind to Epo receptors.
2. Which of the following correctly describes an aspect of the physiology of Epo in the brain?
  - A. Epo found in the brain would be all exogenous, having been produced in the kidneys or administered pharmaceutically.
  - B. Hypoxia-inducible factor-1 leads to decreased action of Epo in the brain.
  - C. An overabundance of Epo receptors in the brain has been linked to increased apoptosis.
  - D. Both Epo and Epo receptors are present in the brain during embryogenesis as early as 5 weeks after conception.
  - E. In the nervous system, the only cells that express Epo receptors are neural crest cells.
3. Epo has been studied as a potential neuroprotective agent and may have several mechanisms of action for this purpose. Which of the following best describes one of the mechanisms of neuroprotection?
  - A. Epo may reduce inflammation after injury by stimulating the production of interleukin-1 beta and tumor necrosis factor  $\alpha$ , and decrease levels of interleukin-10.
  - B. Epo has been shown to completely suppress the production of M2 phenotype macrophages and increase the production of M1 macrophages, leading to improved cell balance after injury.
  - C. Epo has been shown to decrease infarct size in animal models of stroke, which may be due to decreased apoptosis from mechanisms such as activation of the *Janus tyrosine kinase 2* pathway.
  - D. Injury during development leads to downregulation of Epo receptors, which leads to a small window of opportunity for exogenous administration to have any beneficial effect.
  - E. Epo administration has been associated with increased caspase-3-positive endothelial cells, particularly with simultaneous treatment with hyperoxia.
4. Clinical studies of Epo in preterm infants has led to several findings for potential benefit and optimizing treatment strategies. Which of the following regarding Epo therapy for preterm infants is correct?
  - A. Adult pharmacokinetics and dosing have been found to be generally appropriate for preterm infant Epo dosing to achieve hematologic goals for decreasing transfusions as well as for neuroprotection.
  - B. In clinical trials designed to investigate transfusion frequency, no significant differences in neurodevelopment have been found between Epo and placebo groups.
  - C. A greater benefit of Epo for neurodevelopmental outcomes may be seen for those preterm infants who have brain injury due to intraventricular hemorrhage.
  - D. A higher than peak serum Epo concentration is associated with lower scores on the Bayley Scales of Infant Development II Mental Developmental Index.
  - E. Executive function, as measured by various parameters, seems to be the same or slightly worse in infants treated with Epo or darbepoetin compared with no treatment.

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5. Epo has been investigated as a potential treatment for term infants with hypoxic-ischemic encephalopathy. Which of the following statements regarding this area of investigation is correct?
- A. A study by Zhu and colleagues investigating moderate or severe hypoxic-ischemic encephalopathy randomizing patients to receive Epo or conventional treatment found a benefit of Epo in reducing the outcome of moderate/severe disability or death.
  - B. Elmahdy and colleagues found that serum nitric oxide levels were not detectable in infants with mild to moderate hypoxic-ischemic encephalopathy who received Epo.
  - C. In a study by El Shimi and colleagues comparing therapeutic hypothermia and Epo for hypoxic-ischemic encephalopathy, the Epo group had significantly higher survival at hospital discharge, 3 months, and 1 year of age.
  - D. Wu and colleagues have performed several studies showing that the combination of therapeutic hypothermia and Epo administration may be counterproductive, leading to worse outcomes than just using 1 of the treatment strategies.
  - E. Baserga and colleagues have performed several studies comparing darbepoetin and Epo, determining that Epo may be optimal for infants due to the ability to give fewer doses and the higher efficacy.

## Update on Erythropoiesis-Stimulating Agents Administered to Neonates for Neuroprotection

Jessie R. Maxwell and Robin K. Ohls

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# Intraventricular Hemorrhage and White Matter Injury in Preclinical and Clinical Studies

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## Education Gaps

1. Clinicians should be aware of the lack of effective postnatal interventions for the prevention and treatment of germinal matrix–intraventricular hemorrhage.
2. Physician-scientists should design studies evaluating prevention and treatment of germinal matrix–intraventricular hemorrhage in appropriate animal models.

## Abstract

Germinal matrix–intraventricular hemorrhage (IVH) occurs in nearly half of infants born at less than 26 weeks' gestation. Up to 50% of survivors with IVH develop cerebral palsy, cognitive deficits, behavioral disorders, posthemorrhagic ventricular dilatation, or a combination of these sequelae. After the initial bleeding and the primary brain injury, inflammation and secondary brain injury might lead to periventricular leukomalacia or diffuse white matter injury. Potential factors that are involved include microglia and astrocyte activation, degradation of blood components with release of "toxic" products, infiltration of the brain by systemic immune cells, death of neuronal and glial cells, and arrest of preoligodendrocyte maturation. In addition, impairment of the blood-brain barrier may play a major role in the pathophysiology. A wide range of animal models has been used to explore causes and mechanisms leading to IVH-induced brain injury. Preclinical studies have identified potential targets for enhancing brain repair. However, little has been elucidated about the effectiveness of potential interventions in clinical studies. A systematic review of available preclinical and clinical studies might help identify research gaps and which types of interventions may be prioritized. Future trials should report clinically robust and long-term outcomes after IVH.

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### ABBREVIATIONS

A1M	alfa-1-microglobulin
AQP1	aquaporin 1
BBB	blood-brain barrier
CPE	choroid plexus epithelium
CSF	cerebrospinal fluid
DFX	deferrioxamine
GM	germinal matrix
GMH	germinal matrix hemorrhage
hA1M	human plasma alfa-1-microglobulin
Hb	hemoglobin
Hp	haptoglobin
ICH	intracranial hemorrhage
IGF-1	insulinlike growth factor 1
IVH	intraventricular hemorrhage
MMP	matrix metalloproteinase
MSC	mesenchymal stem cell
NKCC	Na/K/Cl cotransporter
PAR	protease-activated receptor
PHVD	posthemorrhagic ventricular dilatation
rA1M	recombinant human alfa-1-microglobulin
rEPO	recombinant erythropoietin
SPAK	Ste20-type stress kinase
TGF- $\beta$	transforming growth factor $\beta$
TLR	Toll-like receptor
VEGF	vascular endothelial growth factor
WM	white matter

## Objectives After completing this article, readers should be able to:

1. Recognize the multiple causes and mechanisms leading to germinal matrix–intraventricular hemorrhage.

## 2. Describe the main effects of different interventions for the prevention and treatment of germinal matrix–intraventricular hemorrhage observed in preclinical and clinical studies.

### INTRODUCTION

Intraventricular hemorrhage (IVH) continues to be a serious problem worldwide despite the progress of perinatal/neonatal medicine. Approximately one-third of preterm infants are affected by IVH, and as many as 45% of infants born at less than 26 weeks' gestation are affected. (1)(2) It has been reported that up to 50% of survivors with IVH develop cerebral palsy, cognitive deficits, behavioral disorders, posthemorrhagic ventricular dilatation (PHVD), or a combination of these outcomes. (3) Indeed, a meta-analysis suggests that even a germinal matrix hemorrhage (GMH) without parenchymal damage may affect long-term neurodevelopmental outcome. (4)

The early pathophysiological response associated with a GM-IVH induces the primary brain injury, followed by inflammation and secondary brain injury such as periventricular leukomalacia or diffuse white matter (WM) injury. The exact mechanisms of secondary brain injury after germinal matrix (GM)–IVH remain unknown. Several factors are involved, including microglia and astrocyte activation, degradation of blood components with release of “toxic” products, infiltration of the brain by systemic immune cells, death of neuronal and glial cells, and arrest of preoligodendrocyte maturation. Altogether, these events are associated with dysfunction of the blood-brain barrier (BBB). It is important to understand the possible mechanisms and triggers involved in the development of GM-IVH to identify possible approaches for prevention. Furthermore, understanding GM-IVH–induced secondary brain injury is a key factor for the development of efficient treatment strategies.

### IVH MODELING

#### Animal Models

GM-IVH is a complex and multifactorial disease whose pathogenesis is not completely understood. Hemorrhage originates in the GM, and with further rupture of the ventricular ependyma, it may evolve into an IVH. (5) Due to its complexity, a variety of animal models of IVH have been used, involving different animal species, including mice, rats, rabbits, cats, dogs, sheep, pigs, and primates (Table 1). Most of the animal studies on IVH have focused on

treatment rather than on prevention. The paucity of studies addressing prevention may be due to the fact that prematurity per se is such a strong risk factor for GM-IVH and prevention of preterm birth remains an unsolved issue. Most of the animal models described herein represent a mature systemic physiology coupled with a brain maturity that varies from extremely preterm to term compared with that of the human. The absence of actual preterm birth in these models disregards the interaction between important aspects of immaturity, such as trophic deprivation and coagulation impairment, and GM-IVH in the immature brain. With this central shortcoming in mind, these models still provide important information concerning IVH development, IVH-induced secondary brain injury, and possible treatment strategies.

One of the most common methods of inducing IVH in animals is by injecting centrifuged blood with an elevated hematocrit level into the ventricular space. This model has been used in rats, mice, and piglets, (6)(7)(8)(9)(10) with IVH developing in up to 70% of animals. This model can help investigate the role of blood components in PHVD formation and in WM damage. However, several limitations are present in these models. Postnatal day 7 in rodents and term age in piglets are considered appropriate time points for perinatal injury studies because the brain growth velocity is at its peak. (25) However, other organs are mature, which disregards important aspects of the clinical situation of preterm birth per se. Second, neither rodents nor piglets bleed spontaneously in the GM, suggesting that the inherent fragility of the GM vasculature is not present in these species. (26) Third, because the GM vasculature is intact, small periventricular infarctions, as observed in humans with periventricular hemorrhagic infarction, do not occur. (19)(26) In addition, corticospinal tract myelination is relatively advanced in rodents and piglets at these ages of brain maturation, rendering them more resistant to injury. (25)

Another commonly applied way of inducing intracerebral hemorrhage in rodent models aiming to mimic preterm human IVH is by performing stereotactic injection of collagenase. Collagenase is a proteolytic intracellular enzyme that catalyzes the hydrolysis of collagen. Because collagen is a fundamental component of the basal lamina of blood vessels, administration of collagenase into the brain

TABLE 1. Most Commonly Used Animal Models of GM-IVH

MODEL OF GM-IVH INDUCTION	ANIMAL	CLINICAL COMPARISON	MECHANISMS INVESTIGATED	REF. NO.
Centrifuged blood with high hematocrit, intracerebroventricular injection	Rodents Piglets	Brain development is comparable with gestational week 32 in human preterm newborn, myelination is advanced, other organ systems are mature	Role of blood components and erythrocyte lysis, immune response, integrity of BBB, neural-vascular unit damage	6-10
Collagenase injection into GM	Rodents	Brain development is comparable with gestational week 32 in human preterm newborn, myelination is advanced, other organ systems are mature	Brain morphology Neurodevelopmental outcome	11-15
Hypercarbia, hypertension, hypotension followed by rapid volume expansion	Dogs	GM layer is comparable with preterm humans, but the brain is overall mature, differences in cerebral perfusion	Role of cerebral blood fluctuations as causative mechanism	16-18
Intraperitoneal injection of glycerol to induce hyperosmolality	Preterm rabbits	Brain development corresponds to gestational week 24-25 in humans and cerebellum to gestational week 22-23 in humans, GM fragility is comparable with human preterm newborns, organ systems are immature	Role of extracellular hemoglobin and its metabolites, neuroinflammation, myelination, vascular fragility, neurocognitive and morphologic changes	19-21
Genetic models	Knockout rodents	Knockout mice embryos, mortality is nearly 90% shortly after birth, still challenging to create a model of spontaneous GM-IVH	Overexpression of VEGF, semidominant mutation of procollagen type IV $\alpha 1$ , lack of $\alpha v$ integrin	22-24

BBB=blood-brain barrier, GM-IVH=germinal matrix-intraventricular hemorrhage, VEGF=vascular endothelial growth factor.

dissolves the extracellular matrix surrounding the capillaries, thus opening the BBB, and leads to intracranial bleeding. (11)(12)(13) In the collagenase model, neurocognition seems to be affected in a manner comparable with human infants. Moreover, similar to human infants, brain volumes are reduced after bleeding. (14)(15) However, it is known that collagenase induces a notable inflammatory response at the injection site that might affect the findings. (14) Unfortunately, data on morphologic changes in this particular model are lacking. A major disadvantage with this model is that the localization of the induced bleeding in this model does not correspond to that of preterm GM-IVH, with hemorrhages mainly being induced in periventricular tissue and basal ganglia. Although, this model is interesting and reproducible, it has obvious limitations.

It has been suggested in clinical studies that lack of cerebral blood flow autoregulation, rapid volume expansion, and hypercarbia may increase the risk of IVH occurrence. (5) Indeed, GM-IVH was induced in newborn beagle pups by provoking circulatory hypotension followed by rapid volume expansion. This model has led to the understanding that

blood flow fluctuations are important in the pathogenesis of IVH, (16)(17)(18) which has influenced clinical practice.

Another animal model of IVH has been described in premature rabbit pups. (19)(20) Rabbit pups are delivered 3 to 4 days before term (full term = 32 days), and IVH is induced by intravascular hyperosmolality via a postnatal intraperitoneal injection of glycerol. Of note, up to 10% of premature pups bleed spontaneously in the ventricles. (19) Moreover, the animals do exhibit signs of respiratory distress syndrome, as evident by tachypnea and intercostal and subcostal retractions, but do not require interventions supporting respiratory function. Brain development at gestational day 29 in the rabbit corresponds to approximately gestational week 24 or 25 in human infants for cerebrum formation and to week 22 or 23 for cerebellum formation. (19) Altogether, the rabbit glycerol model presents essential similarities to IVH in human preterm infants and includes immaturity of other organs as well. In this animal model, both behavioral deficits and morphologic changes have been described, such as neuroinflammation, periventricular cell death, preoligodendrocyte death, arrest of myelination, and



axonal damage. (19) It has been shown that extracellular hemoglobin (Hb) plays a crucial role in WM damage as it spreads widely across the WM tracts of the brain. (21)(27) Extracellular Hb and its metabolites may lead to a chronic persisting inflammation with long-term consequences for WM development after IVH.

All the animal IVH models reported previously herein lead to the development of PHVD.

Some genetic models of IVH have also been developed. In a spontaneous GM-IVH transgenic mouse embryo model, vascular endothelial growth factor (VEGF) overexpression is induced specifically in the GM via the tetracycline regulatory system. (22) VEGF is a central factor in angiogenesis, and its overexpression in the GM leads to an outgrowth of weak vasculature that is prone to rupture. In this model, there was a 90% incidence of spontaneous intracranial hemorrhage (ICH) that extended into the ventricles; however, a critical disadvantage of this model is the high mortality (approximately 80% of embryos die before birth). In another genetic mutation model characterized by a semidominant mutation in procollagen type IV alpha 1, ICH and death occurred within 1 day of birth. (23) McCarty and colleagues (24) found that the mice lacking  $\alpha v$  integrin developed ICH in utero and died soon after birth. Thus, genetic models of GM-IVH illustrate important aspects of IVH evolution but present limitations for the study of short- and long-term outcomes.

### In vitro Models

There are currently no in vitro models that resemble IVH. Nevertheless, different cell culture techniques have been used to investigate the effect of clot-derived factors, such as thrombin, Hb and its metabolites, iron, and thrombin.

## PREVENTION

The major risk factor for the development of GM-IVH in humans is premature birth because the GM involutes almost completely by gestational week 36 in human infants. (5) Preventing preterm birth is a complicated area of research and has been reviewed elsewhere. (28) However, due to a significant improvement in perinatal medicine, the survival of extremely preterm infants is increasing worldwide. Nonetheless, the incidence of IVH has remained nearly the same during the past 2 decades despite increased absolute numbers of IVH. (1)(2)(29)

The GM vasculature exhibits unique characteristics explaining its propensity for rupture. The endothelial proliferative rate in the GM is extremely high, coupled with a high expression of VEGF and angiopoietin-2. (5) In addition,

the GM, compared with other cerebrovascular regions, has a lower number of pericytes, decreased presence of transforming growth factor  $\beta$  (TGF- $\beta$ ), and lower expression of fibronectin-1 in basal lamina. (5) In line with these findings, prenatal administration of angiogenic inhibitors in the preterm rabbit model decreased the incidence of GMH. (30) Thus, by suppressing proliferation and increasing vascular maturation in the GM, the incidence of GMH may be reduced in preterm infants. Interestingly, treatment with insulinlike growth factor 1 (IGF-1) in complex with IGF binding protein-3 seemed to decrease the rate of severe IVH in extremely preterm infants. (31) These effects may relate to a maturational effect of administered IGF-1/IGFBP-3 on GM vasculature.

As mentioned previously herein, extremely preterm infants undergo rapid changes in cerebral blood flow after birth, and this has been reported in the beagle IVH model. (16)(17)(18) It has been suggested that care strategies initiated in the delivery room aiming to reduce hemodynamic fluctuations might reduce the risk of GM-IVH. Delayed cord clamping is another intervention in the immediate postnatal period that has been shown to have an effect on the incidence of GM-IVH, reducing its occurring risk. (32) One could speculate that an increased circulating blood volume in infants receiving delayed cord clamping has a stabilizing effect on cerebral blood flow; in addition, delayed clamping may have an enhancing effect on the BBB by transfusing stem cells, growth factors, exosomes, microvesicles, and anti-inflammatory substances. Finally, delayed cord clamping may improve hemostasis by transfusion of coagulation factors, platelets, and Hb scavengers. Animal studies of delayed cord clamping may elucidate the mechanisms involved in diminishing the risk of IVH.

## GM-IVH-INDUCED BRAIN INJURY

Brain injury after IVH may be divided into 2 different phases: the primary injury, when actual bleeding occurs, and the secondary injury, which is induced by neuroinflammation. Most of the preclinical research studies have examined the secondary brain injury, with a particular focus on WM injury.

### Primary Injury

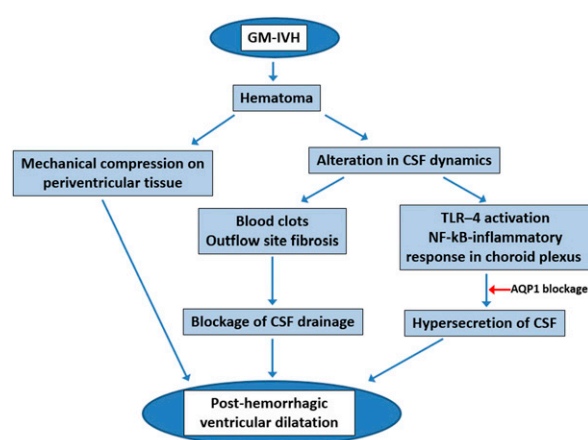
**Physical Effect of IVH.** There are at least 3 physical effects of IVH: displacement of neural tissue (mass effect), increased intracranial pressure, and blockage of cerebrospinal fluid (CSF) pathways. Once bleeding occurs there is a mechanical effect on the ventricular wall, including direct stretching of the wall and the periventricular tissue along the ventricles. There are no preclinical data available addressing the

physical impact of the space-occupying hematoma. However, neurophysiological assessments in preterm infants with IVH who are subsequently diagnosed as having PHVD have demonstrated an early alteration in visual evoked potentials and amplitude-integrated electroencephalography, which normalize as soon as effective PHVD treatment is started (evacuation of CSF). (33)(34)

Another potential physical effect of IVH is the transient blockage of the CSF drainage pathway, (35) either in the ventricular system or at the CSF outflow sites (Fig 1). It is hypothesized that this blockage may contribute to the development of PHVD. Furthermore, a physical block by blood clots and outflow site fibrosis may lead to a further alteration of CSF homeostasis. A classical model of CSF dynamics postulates that the development of PHVD requires obstruction of CSF flow from the ventricles and/or impairment of the arachnoid granulations: these might be classified as a primary decrease in CSF reabsorption. However, this hypothesis, which is supported by limited experimental evidence, (36) neglects the potential role of increased CSF secretion in disease pathogenesis. (37) Indeed, hypersecretion of CSF after IVH seems to depend on Toll-like receptor (TLR) 4 activation and nuclear factor  $\kappa$ B-dependent inflammatory response in the choroid plexus epithelium (CPE). This leads to activation of Ste20-type stress kinase (SPAK) and further phosphorylation and activation of Na/K/Cl cotransporter (NKCC) 1 at the apical surface of the CPE (Fig 1). (37) In fact, genetic depletion of TLR4 or SPAK restores hyperactive CSF secretion rates and improves PHVD symptoms. Similarly, treatment with inhibitors of TLR4–nuclear factor  $\kappa$ B signaling or the SPAK–NKCC1 complex reduces the hypersecretion of CSF, thereby diminishing by PHVD and its related symptoms. (37) Further studies targeting TLR4 and SPAK pathways are warranted.

**Mass Effect.** Clearing the hematoma after IVH may reduce the mass effect and be useful for decreasing levels of toxic substances in the brain. (38)(39)(40)(41)(42) Fibrinolytic therapy does not reduce death or need for a ventriculoperitoneal shunt. (43) Although fibrinolytic therapy has been shown to increase the incidence of secondary hemorrhage, the long-term DRIFT (drainage, irrigation, and fibrinolytic therapy) study at age 2 years showed reduction of severe disability or death and improvement of cognitive function in preterm infants with severe IVH and PHVD. (43) To our knowledge, there are no ongoing preclinical studies in newborn IVH models that examine the efficacy and safety of fibrinolytic therapy.

**Alterations in CSF Homeostasis.** Hyperproduction of CSF occurs after IVH. Approximately 80% of CSF is secreted by CPE, (44)(45)(46) whereas the remaining



**Figure 1.** Impact of hematoma in germinal matrix–intraventricular hemorrhage (GM-IVH). AQP1=aquaporin 1, CSF=cerebrospinal fluid, NF- $\kappa$ B=nuclear factor  $\kappa$ B, TLR=Toll-like receptor.

20% originates from the brain interstitial fluid and indirectly from the BBB. (47) The estimated surface area of the human BBB (20 m<sup>2</sup>) (48) exceeds the surface area of the CPE, which is estimated to be 0.02 m<sup>2</sup> (49); accounting for the surface extension of microvilli, the CPE surface may maximally extend to 5% of the BBB area. Nonetheless, because the BBB has a low permeability to ions and water, the expected high transport rate of CPE might be sufficient to explain CSF production. However, there are some controversies about this central paradigm, as discussed elsewhere. (46)(50)(51)(52)(53)

One of the possible treatment strategies for PHVD could be normalization of the CSF secretion rate. The CPE contains tight junctions and a wide range of ion transporters and water channels (aquaporin 1 [AQP1]), which can be altered. This was the rationale to assess the effect of 2 diuretics in human clinical trials of IVH: a combination of acetazolamide (a carbonic anhydrase inhibitor) and furosemide (an Na/Cl cotransport inhibitor). This therapy was effective for reducing CSF secretion, but it did not decrease the need for ventriculoperitoneal shunt placement and actually increased the neurologic morbidity. (54)(55)(56) There are no preclinical studies on the use of these diuretics in animals with PHVD, except for a recent investigation demonstrating mild reduction of CSF production in the rat with PHVD. (37) AQP1 is extremely important for water transcellular transport, and AQP1 knockout mice have an approximately 80% reduction in water permeability from CPE. (57) Moreover, there is a concomitant decrease in the CSF secretion rate by 35% by CPE, (57) which is nearly 50% of the total CSF secretion rate because CPE secretes only 70% to 80% of the CSF. It seems that AQP1 may have a central role in CSF formation; however, it is unclear to what extent AQP1 mediates the transepithelial water transport.

Surprisingly, there are not much data available on how IVH affects water transport in the choroid plexus. Sveinsdottir et al (58) demonstrated an increase in choroid plexus AQP1 protein expression in a preterm rabbit IVH model (Fig 1). More studies are needed to understand the possible role of AQP1 in PHVD development after IVH. It seems that targeting AQP1 may represent a possible treatment strategy.

## Secondary Injury

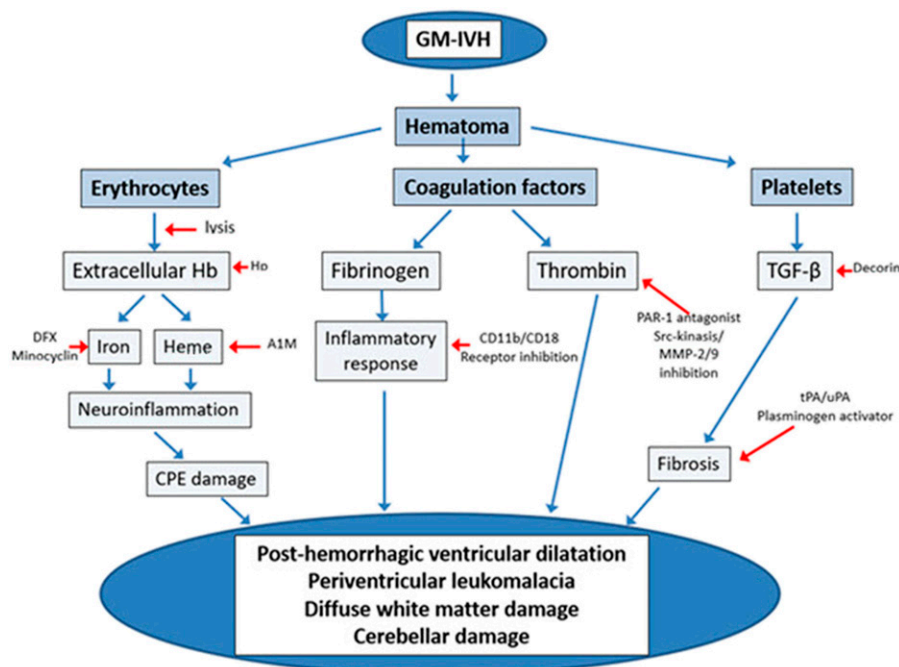
**Blood Components and Brain Injury.** Figure 2 depicts an overall picture of the mechanisms involved in secondary brain damage after IVH and potential therapeutic targets.

A considerable amount of research in this area has indicated that secondary brain injury might be caused by blood components. Once IVH occurs, erythrocytes undergo hemolysis with release of extracellular Hb and its degradation products that are toxic to the immature brain. Moreover, other blood components (eg, coagulation factors) and immune cells can independently induce/aggravate brain damage. Studies on blood component-based mechanisms of secondary brain injury have led to the identification of potential therapeutic targets. The following section examines the mechanisms of blood-derived toxicity.

**Hemolysis, Hb, and Its Degradation Products.** After IVH in preterm infants, there is deposition of blood in the

intraventricular space, followed by lysis of erythrocytes, resulting in a subsequent release of extracellular Hb into the CSF. (27) Extracellular Hb is highly reactive and rapidly oxidized from ferrous ( $\text{Fe}^{2+}$ , denoted oxyHb) to ferric ( $\text{Fe}^{3+}$ , denoted metHb) Hb, (27)(59) which readily releases the heme group. (60) Free heme, iron, and oxygen are highly redox reactive and can damage lipids, proteins, and DNA through oxidative modification, cross-linking, and fragmentation. (60) Heme binds to lipids of cell membranes, leading to toxic cytolytic effects through both oxidative and nonoxidative mechanisms. (61) In addition to its redox-related effects, heme has been described to act as a damage-associated molecular pattern molecule that triggers TLR-mediated proinflammatory damaging pathways. (62)(63)(64) Moreover, extracellular Hb causes structural damage of the CPE as soon as 24 hours after IVH in preterm rabbit pups and results in severe cellular disintegration with loss of normal villous morphology and signs of cellular apoptosis and necrosis 72 hours after IVH. (27)(65) Furthermore, it has been shown in animal studies that extracellular Hb activates the inflammatory cascade, resulting in elevation of tumor necrosis factor  $\alpha$  in the CSF. (27) The elevation of tumor necrosis factor  $\alpha$  IVH was identified in preterm human infants as well. (27)

Iron is another product that is released in abundance after IVH and erythrocyte lysis and is involved in the



**Figure 2.** Pathological mechanisms underlying the formation of posthemorrhagic ventricular dilatation, periventricular leukomalacia, and white matter and cerebellar damage. A1M=alfa-1-microglobulin, CPE=choroid plexus epithelium, DFX=deferoxamine, Hb=haptoglobin, Ho=haptoglobin, MMP=matrix metalloproteinase, PAR=protease-activated receptor, TGF- $\beta$ =transforming growth factor  $\beta$ , tPA/uPA=tissue and urokinase plasminogen activator.

secondary brain damage during IVH and PHVD development. (66) Non-protein-bound iron and ferritin deposit in ependymal lining after neonatal IVH. (67)(68) Interestingly, non-protein bound iron was found in the CSF of preterm infants with PHVD. (69) In animal IVH rat models, iron deposition after IVH already occurs in the first day, and upregulation of brain ferritin lasts for several weeks. (66) The deposition of iron along the ventricular ependyma may lead to denudation areas in the lining, facilitating the movement of extracellular Hb deeper into the periventricular tissue and resulting in diffuse WM injury. Indeed, a wide distribution of extracellular Hb was found in both adjacent periventricular tissue and deeper in WM tracts involving the corpus callosum, corona radiata, subthalamic regions, and hippocampus in the preterm rabbit pup IVH model. (21) Periventricular tissue is characterized by a high presence of preoligodendrocytes, which progressively differentiate to mature oligodendrocytes. This process is extremely important for normal WM development, and alterations may lead to diffuse WM damage and periventricular leukomalacia that are found in premature infants. This process is particularly active between weeks 23 and 35 of gestation. (70)(71) Preoligodendrocytes are highly vulnerable to oxidative stress, inflammation, and hypoxic-ischemic events. (70)(71) In addition to periventricular distribution, extravasation of red blood cells and Hb into the CSF have been shown to result in deposition of Hb metabolites on the cerebellar surface, leading to alteration of normal development of the cerebellar cortex and its related functions. (72)(73)(74) Furthermore, the causal involvement of extracellular Hb in compromised cerebellar neuronal progenitor proliferation and delayed Purkinje cell maturation after IVH has been reported. (74)

**Hemolysis, Hb, and Its Degradation Products—Possible Treatment Targets.** As described previously herein, data suggest that extracellular Hb and its degradation products play a central role in secondary brain damage after IVH. Thus, targeting extracellular Hb and its metabolites may represent valuable treatment strategies. Physiologically, several endogenous systems are involved in the neutralization of extracellular Hb and its degradation products, such as haptoglobin (Hp), high- and low-density lipoproteins, serum albumin, and hemopexin.

Hp is crucial to prevent extra-erythrocytic Hb-induced injury because of its high binding affinity for extracellular Hb. Hp is synthesized mainly in the liver and is an acute phase protein. (75) The key role of Hp is to clear the intravascular extracellular Hb. Hp binds to extracellular Hb, forming a stable Hb–Hp complex, which then funnels the Hb molecules for intracellular endocytosis. (76)(77) Intracellularly, the

enzyme heme oxygenase 1 breaks down heme to bilirubin and carbon monoxide, which have antioxidant and vasodilatory properties. (78) By forming a tight complex with extracellular Hb, Hp stabilizes and shields heme iron in the hydrophobic pocket of Hb, thereby preventing its cytotoxic and pro-oxidative damage. (79) Therefore, the elimination of extracellular Hb from the extracellular environment by the formation of Hb–Hp complexes reduces the interaction of extracellular Hb with the brain's innate immune system cells signal-transducing receptors and, thereby, diminishes exposure to iron overload and to heme-induced toxicity. After intracerebral hemorrhage, oligodendroglial cells start to produce Hp, (80) thereby protecting axons from damage imposed by hemolytic products. Mice overexpressing Hp showed better preservation of axonal integrity after ICH. (80) Importantly, Hp-overexpressing oligodendrocytes in culture showed reduced loss of myelin basic protein on exposure to hemolytic products compared with oligodendroglia from Hp-deficient mice. (80) This recent finding is of extreme importance considering the role of oligodendrocytes in diffuse WM injury after IVH, thus representing a potential treatment strategy. In fact, Hp knockout mice had a worse neurologic outcome after ICH, whereas overexpression of Hp was neuroprotective. (80)

However, the local production levels of Hp may be insufficient to fully scavenge extracellular Hb. (81) Galea et al (81) demonstrated that after adult subarachnoid hemorrhage, the Hb–Hp system was quickly saturated with a residual inability to handle extracellular Hb, indicating an insufficient Hb scavenging capacity in the brain. Indeed, in premature rabbit pups that underwent intraventricular administration of Hp, there was a partial reduction in the Purkinje cell maturational arrest caused by IVH, which in turn related to decreased impairment of the proliferative portion of the external granular layer after IVH. (74)

Despite multiple positive effects of Hp on preservation of secondary brain damage after IVH, a recent in vitro study showed that Hb could be toxic to the neurons in an Hp-dependent manner because of a lack of iron-sequestering systems that may lead to iron overload intracellularly. (82) Intracellular iron is free to react with available hydrogen peroxide to form radical oxygen species, resulting in induction of apoptotic cascade and cell death. (82) Additional well-designed studies are needed to detect possible beneficial and detrimental effects of Hb scavenging through administration of Hp.

Deferoxamine (DFX) is a ferric-iron chelator that is used clinically for acute iron poisoning, systemic iron overload, and hemochromatosis. It has been suggested that DFX may attenuate the brain injury and improve neurologic outcome after IVH/ICH. (83) However, the authors of the systematic

review on DFX effects in animal IVH/ICH models raise concerns about the low quality of the study and possible publication bias, concluding that DFX neuroprotective effects need to be further assessed. (83) Beneficial effects of DFX after IVH/ICH include reduction in iron overload-induced edema, (84) cell death and neuronal degeneration in periventricular tissue, (8)(66)(85)(86) hippocampal degeneration, (8) and inflammation. (84)(85)(87) One of the phase 2 clinical trials in adults with ICH treated with either DFX or placebo was suspended due to an increased incidence of acute respiratory distress syndrome. (88) The authors decreased the dosage of DFX and conducted a double-blind multicenter phase 2 study in adult ICH. (89) The treatment was considered to be safe, but it did not improve neurologic outcomes of patients with ICH. Longer follow-up is needed. Another ongoing phase 2 study is registered to assess the effects of DFX and xingnaojing injection treatment in intracerebral hemorrhage. (90)

Another potential treatment strategy might be minocycline, which is a tetracycline antibiotic used to treat infections, rheumatoid arthritis, and acne. It has good BBB penetration, chelates iron, inhibits microglia, and reduces apoptosis and inflammation. (91)(92)(93) Minocycline may diminish iron accumulation in an experimental GM-IVH model, resulting in alleviation of brain edema, PHVD, and cell death. (94) Minocycline is thought to suppress ferritin upregulation after hemorrhage by acting through the cannabinoid receptor 2, inhibiting the inflammatory cascade. (94) In a small, clinical phase 2 study in an adult population after ICH, it has been shown that minocycline is safe; however, no difference in inflammation markers (matrix metalloproteinase [MMP]-9, interleukin-6, iron, ferritin, total iron-binding capacity), ICH volume, or perihematomal edema in patients treated with minocycline were detected compared with the control group. (95) An ongoing phase 2 study on the effects of minocycline after ICH in adults has been registered. (96)

Another potential treatment target strategy for IVH is the heme and free radical scavenger alfa-1-microglobulin (A1M). A1M has been demonstrated to be a potent tissue-protective protein that mediates its effects through heme binding, reductase activity, radical scavenging, and binding to mitochondria. (97)(98) Mitochondrial uptake of A1M in the early stages of cell death results in inhibition of heme- and reactive oxygen species-induced mitochondrial swelling. (99) A recombinant human A1M (rA1M) has been developed (100)(101) and has been shown to be functionally equivalent to endogenous A1M derived from human plasma (hA1M). (102)(103) The brain has a minimal production and systemic distribution of endogenous A1M, reflected in the

trace quantities of the protein present in CSF compared with other body fluids: CSF, 0.0423 mg/L; serum, 44.2 mg/L; synovial fluid, 20.8 mg/L; ascites, 28.7 mg/L; pleural effusion, 21.5 mg/L; and amniotic fluid, 0.0027 mg/L. (104) Interestingly, an increase in the concentration of endogenous A1M in CSF after ICH has been documented in adult human patients. The increase was associated with serum infiltration as a result of BBB disruption; however, local production could not be excluded. (105)

Based on the pathophysiological mechanisms described for brain injury after IVH, exogenously administered A1M seems to be a promising treatment alternative. In a preterm rabbit pup IVH study, exogeneously administered rA1M had a wide distribution across brain and cerebellar WM. (106) Moreover, some functional studies detected that hA1M preserved mitochondrial structure and arrested the fusion of mitochondria. (106) Indeed, hA1M administration significantly reduced cellular activation, inflammatory response, and tissue injury, suggesting that administration of hA1M blocks the toxic reactions of extracellular Hb metabolites. (106) More studies are needed to understand the mechanism of action, safety, and beneficial effects of rA1M.

**Coagulation Components.** Besides erythrocytes, plasma components play a role in IVH-induced secondary brain injury. In particular, some of the elements of the coagulation system seem to be involved, including prothrombin/thrombin (factor IIa). Thrombin is formed after the cleavage of prothrombin in the clotting process, which is upregulated during hemorrhage. Thrombin is essential to convert soluble fibrinogen into insoluble fibrin to prevent bleeding. Immediate production of thrombin in the brain occurs after a cerebral hemorrhage or BBB disruption due to brain injury. (107) Indeed, several *in vivo* (108)(109)(110) and *in vitro* (111)(112) studies indicate that a high brain concentration of thrombin may be deleterious. It has been shown that a high concentration of thrombin is involved in brain edema formation and contributes to ischemic brain injury. (113) Furthermore, in high concentrations, thrombin induced neuronal and astrocyte cell death. (112)(113) However, a low brain concentration of thrombin (50–100 nM) is neuroprotective. (111)(114) Such a dichotomy of thrombin in the brain may reflect its multiple functions. It enhances the synthesis and secretion of nerve growth factor in glial cells, modulates neurite outgrowth, stimulates astrocyte proliferation, and modulates the cytoskeleton of endothelial cells. (115) In addition, it potentiates *N*-methyl-D-aspartate receptor function (116) and activates rodent microglia *in vitro*. (117)

Most thrombin functions are mediated through protease-activated receptor (PAR) 1, PAR-3, and PAR-4. (118) PAR-1



activation after IVH results in ependymal wall damage, which may contribute to the development of PHVD. (119) Activated thrombin–PAR-1 system results in activation of the Src family of kinases, which are responsible for the phosphorylation of metalloproteinases, in particular MMP-9, which have been shown to lead to disruption of BBB and induce apoptosis. (120)(121)(122) By using PAR-1 antagonists, injury to the ependymal wall was reduced after IVH. (119) Furthermore, a nonspecific Src family kinase inhibitor PP2 (4-amino-5-(4-chlorophenyl)-7-(*t*-butyl)pyrazolo [3,4-*d*] pyrimidine) stops the development of brain edema and BBB disruption after IVH. (123) Inhibition of MMP-2 and MMP-9 by GM6001 resulted in reduction of brain edema and decreased inflammatory cell infiltration after ICH. (122)

Thrombin-induced inflammation has been linked to TGF- $\beta$ . (124) It is believed that TGF- $\beta$  is released into the CSF after platelet extravasation during IVH, and it may play a role in the formation of obstructive hydrocephalus. (125) In juvenile communicating hydrocephalus clinical studies, it has been shown that decorin, a TGF- $\beta$  antagonist, could reverse ventriculomegaly and WM injury. (126)(127) Nevertheless, further research is necessary to fully elucidate the mechanism by which TGF- $\beta$  is involved in hydrocephalus after IVH.

Fibrinogen (factor I) may also be involved in secondary IVH-induced brain injury. Despite the essential role in conversion of fibrinogen to fibrin for hemostasis, the formed clots may result in obstruction of the normal circulation of CSF. Furthermore, it has been shown that the extravascular presence of fibrinogen is a powerful inflammatory response trigger, activating microglia via the CD11b/CD18 receptor, (128) which may aggravate brain injury.

Although coagulation system elements may play an important role in IVH-induced secondary brain injury, targeting them therapeutically is complicated due to their vital role in hemostasis. The therapeutic window may need to focus on targeting downstream mediators (eg, through thrombin-mediated PAR-1 activation or targeting fibrinogen-mediated microglial activation).

Other blood components may also contribute to IVH-induced secondary brain damage. Recently it has been shown that lysophosphatidic acid, present in serum, can impair ependymal integrity. (129) Lysophosphatidic acid is produced and released by activated platelets. (130) Of note, the role of platelets in IVH-induced secondary brain injury has received very little attention.

## PRECLINICAL FINDINGS ON REPAIR OF INJURY

In addition to the preclinical studies addressing the possible reduction or arrest of IVH-induced secondary

brain injury, other studies have explored the possibility of augmenting brain repair of injured tissue. The main strategies have focused on enhancing neurogenesis, stem cell therapy, and reversal of hyaluronan build-up (Table 2).

Recombinant erythropoietin (rEPO), mainly known for stimulating red blood cell production, displays neuroprotective capabilities and might restore the damage in the GM. (153) This is of particular interest because IVH originates from the GM, which is a source of arising neurons and glial cells in the developing brain. In studies on neonatal hypoxic ischemia, rEPO administration may enhance neurogenesis and oligodendrogenesis (131)(132) and limit inflammation and oxidative stress-induced injury. (133)(134) Administration of rEPO combined with melatonin may reduce ventriculomegaly in the rat pup with IVH. (135) Moreover, the microstructural integrity of WM and gray matter, ultrastructural integrity of ependymal motile cilia, and periventricular lysophosphatidic acid yes-associated protein were restored in treated pups. (135) A large prospective clinical trial of rEPO treatment in preterm infants did not show any benefit on IVH or mortality rates. (136) A similar trial is aiming to investigate the same research question. (137)

Another potential treatment option for IVH might be melatonin, which acts as an antioxidant and free radical scavenger, (138)(139) inhibits free radical-associated red blood cell lysis, (140) decreases neuronal cell death, (141) and decreases hippocampal and nigrostriatal degeneration. (142) In a rat animal IVH model, treatment with melatonin improved neurobehavioral outcomes and reduced the level of brain atrophy. (143)

Stem cell therapies represent a promising treatment approach for IVH. Stem cells were first used to treat intracranial bleeding in adult rats in a collagenase-induced ICH model. (154) Subsequently, it has been shown that treatment with umbilical cord-derived mesenchymal stem cells (MSCs) in an animal ICH model resulted in nerve fiber remyelination, axonal regeneration, and improved neurologic recovery. (155) In a neonatal IVH rat pup model, MSC administration either intracerebrally or intravenously resulted in attenuation of PHVD, better myelination, and better performance on behavioral tests. (144) Indeed, further studies demonstrated that early MSC administration resulted in greater recovery from brain injury. (145) It is suggested that regenerative cells exert their therapeutic benefit through the release of paracrine effects. (156) They promote axon and dendrite growth by secreting mitogenic



TABLE 2. **Preclinical Findings and Ongoing Studies of IVH-Induced Damage Repair**

INTERVENTION	PRECLINICAL DATA	CLINICAL DATA	ONGOING STUDIES
Recombinant erythropoietin	Enhances neurogenesis and oligodendrogenesis, (131)(132) limits inflammation and oxidative stress–induced damage, (133)(134) reduces ventriculomegaly, attenuates microstructure of white and gray matter (135)	Safe, (136) did not decrease IVH incidence or mortality rates (136)	NCT02076373 (137): a randomized controlled trial to investigate the possible protective role of recombinant erythropoietin in preterm infants with IVH
Melatonin	Acts as antioxidant and free radical scavenger (138)(139); inhibits free radical–associated red blood cell lysis, (140) neuronal cell death, (141) hippocampal and nigrostriatal degeneration (142); improves neurobehavioral outcomes and reduces the level of brain atrophy (143)	Not available	Not available
Stem cell–based therapies	Attenuates PHVD, better myelination, better performance on behavioral tests, (144)(145) ameliorates inflammation, (146) enhances angiogenesis, regulates reactive oxygen species production, transfers organelles to injured cells (146)(147)(148)(149)	One phase 1 study (9 premature infants with IVH grade 4): no serious adverse effects or dose-limiting toxicities attributable to mesenchymal stem cell transplant; 5 of 9 infants required shunt derivation. (150) Follow-up assessment is ongoing (NCT02673788 [146]).	NCT02890953 (151): a phase 2 randomized controlled trial, preterm infants with IVH grade 3–4. Primary outcome: death or shunt operation; secondary outcomes: volume ratio of ventricle to whole brain in the brain MRI; death.
Hyalorinidase	Reduces inflammation, increases oligodendrocyte precursor cell maturation, restores myelination in white matter lesions (152)	Not available	Not available

IVH=intraventricular hemorrhage, MRI=magnetic resonance imaging, PHVD=posthemorrhagic ventricular dilatation.

growth factors (brain-derived neurotrophic factor, stromal cell–derived factor 1, and nerve growth factor) known to enhance proliferation, migration, and differentiation of native neuronal progenitor/stem cells. (147)(148)(149) Of note, cell-based therapies have been demonstrated to ameliorate inflammation (interleukin-1 $\beta$ , interferon- $\gamma$ ) by modulating the function of immune cells such as T and B cells, macrophages, and dendritic cells. (146) In addition, they may enhance angiogenesis (VEGF, IGF-1), regulate reactive oxygen species production, and even transfer organelles to injured cells. (146)(147)(148)(149) To date, 1 phase 1 study was performed on 9 preterm infants with a diagnosis of IVH grade 4; no serious adverse effects or dose-limiting toxicities attributable to MSC transplant were identified. (150) No infants died during the study period. Five of 9 infants required shunt derivation. (150) The follow-up assessment (2 years of age) is currently ongoing. (157) Moreover, a phase 2 trial is planned to randomize preterm infants with IVH grade 3–4 to direct intracerebroventricular injection of either MSCs or normal saline. (151)

After IVH, a formation of hyaluronan in WM lesions has been linked to inhibition of oligodendrocyte precursor cell maturation and myelination. Hyaluronan is a glycosaminoglycan polymer that inhibits remyelination. (158) In the preterm rabbit IVH model, hyaluronidase treatment reduced inflammation, increased oligodendrocyte precursor cell maturation, and restored myelination in the WM lesions. (152)

## CONCLUSIONS

GM-IVH is a complex brain condition in the preterm newborn that may lead to long-term neurodevelopmental impairment. Currently, no clear-cut effective prevention or treatment is available for these infants. Preclinical data have identified potential mechanisms for reducing IVH-induced brain damage and enhancing brain repair. Systematic reviews of preclinical studies in adequate animal models and of randomized clinical trials that synthesize the body of evidence is important to highlight the research gaps that should be investigated.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the risk factors for development, proposed mechanisms, clinical and laboratory features, and diagnosis of periventricular-intraventricular hemorrhage.
- Know the proposed prevention strategies, evolution, early complications, management, and long-term consequences of periventricular-intraventricular hemorrhage.
- Know the risk factors for development, proposed mechanisms, clinical and laboratory features, and diagnosis of intraparenchymal cysts/periventricular leukomalacia, and intraparenchymal echodensities.
- Know the pathogenesis, clinical and imaging features, diagnosis, management, and outcomes associated with perinatal cerebral and cerebellar infarction.

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1. Intraventricular hemorrhage (IVH) is a serious complication of prematurity and affects approximately one-third of preterm infants. The incidence of IVH increases at lower gestational ages. What is the incidence of IVH in infants born at less than 26 weeks' gestational age?
  - A. 15%.
  - B. 25%.
  - C. 35%.
  - D. 45%.
  - E. 55%.
2. IVH can lead to significant long-term neurodevelopmental impairments. The pathophysiology of IVH is multifactorial and includes the unique features of the germinal matrix (GM) vasculature. Which of the following statements regarding the GM vasculature is CORRECT?
  - A. The endothelial proliferative rate in GM is low.
  - B. There is high expression of vascular endothelial growth factor in the GM endothelium.
  - C. The GM has a lower number of pericytes compared with other brain regions.
  - D. The levels of transforming growth factor are decreased.
  - E. The basal lamina exhibit lower expression of fibronectin-1 compared with other brain regions.
3. Brain injury after IVH occurs in 2 phases. At the time of bleeding (primary phase), brain injury is due to the physical effects of IVH as well as alterations in cerebrospinal fluid (CSF) homeostasis. Which of the following statements regarding the impact of IVH on CSF homeostasis is INCORRECT?
  - A. Outflow site fibrosis is a mechanism of CSF drainage blockage.
  - B. Hypersecretion of CSF after IVH occurs in 50% of affected infants.
  - C. Activation of Toll-like receptor 4 after IVH contributes to CSF hyperproduction.
  - D. The inflammatory response in the choroid plexus epithelium results in activation of the Na/K/Cl cotransporter 1.
  - E. Aquaporin 1, located in the choroid plexus epithelium, is an important channel regulating the CSF secretion rate.
4. Multiple mechanisms contribute to secondary brain injury after IVH. Which of the following statements regarding the secondary phase of brain injury after IVH is CORRECT?
  - A. The presence of extracellular hemoglobin leads to the rapid oxidation of ferrous iron ( $\text{Fe}^{2+}$ ) to ferric iron ( $\text{Fe}^{3+}$ ), a highly redox reactive compound directly linked to lipid, protein, and DNA damage.
  - B. Free heme can bind to lipids in the cell membrane, leading to toxic cytolytic effects through both oxidative and nonoxidative mechanisms.
  - C. Extracellular hemoglobin has been shown to cause structural damage to the choroid plexus epithelium within 1 hour of injury.
  - D. Loss of normal villous morphology with cellular apoptosis and necrosis can be seen within 72 hours of injury in preterm rabbits.
  - E. Free heme has been shown to activate Toll-like receptor-mediated proinflammatory pathways.

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5. The promotion of brain repair after IVH is 1 of the therapeutic strategies currently under investigation. Which of the following statements regarding brain repair strategies in preclinical models is CORRECT?

- A. The mechanisms of neuroprotection after recombinant erythropoietin administration include enhanced neurogenesis and oligodendrogenesis.
- B. Melatonin acts as an antioxidant and free radical scavenger, and has been shown to decrease brain atrophy in a rat model of IVH.
- C. Treatment with mesenchymal stem cells has been shown to decrease post-hemorrhagic ventricular dilatation in a rat model of IVH.
- D. Mesenchymal stem cell administration has been shown to promote axon and dendrite growth.
- E. Treatment with hyaluronidase limits inflammation and oxidative stress.

# Intraventricular Hemorrhage and White Matter Injury in Preclinical and Clinical Studies

Olga Romantsik, Matteo Bruschetti and David Ley

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# Multiple Organ Dysfunction During Therapeutic Cooling of Asphyxiated Infants

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## Education Gaps

The primary focus of the published cooling trials has been to reduce the adverse neurodevelopmental outcomes associated with hypoxic-ischemic encephalopathy. There is a lack of understanding of how therapeutic cooling affects the function of the multiple organ systems that have already undergone injury induced by perinatal asphyxia.

## Abstract

The main purpose of therapeutic cooling is **neuroprotection** of asphyxiated infants with significant hypoxic-ischemic encephalopathy. However, to improve the overall outcome, it is necessary to properly manage the full range of multiple organ system complications found in asphyxiated infants undergoing therapeutic cooling. Every physiologic process in an asphyxiated infant can potentially be affected by the cooling treatment. The purpose of this review is to discuss the effect of cooling on neonatal physiology in the current recommended cooling range and the management thereof.

**AUTHOR DISCLOSURE** Drs Bhagat and Sarkar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

### ABBREVIATIONS

AKI	acute kidney injury
CI	confidence interval
ECMO	extracorporeal membrane oxygenation
F <sub>IO<sub>2</sub></sub>	fraction of inspired oxygen
HIE	hypoxic-ischemic encephalopathy
MOD	multiple organ dysfunction
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PPHN	persistent pulmonary hypertension
RR	risk ratio
SIADH	syndrome of inappropriate antidiuretic hormone secretion

## Objectives After completing this article, readers should be able to:

1. Recognize the multiple organ system complications commonly found in asphyxiated infants undergoing therapeutic cooling.
2. Describe the effects of cooling treatment across the various organ systems of infants who are already suffering from asphyxia-induced multiple organ hypoxic-ischemic injury.
3. Highlight the management principles of multiorgan system problems that require careful monitoring and substantial supportive care applicable to any asphyxiated infant regardless of cooling.

## INTRODUCTION

Multiple organ dysfunction (MOD) in association with hypoxic-ischemic encephalopathy (HIE) after moderate to severe asphyxia in newborns has been

extensively reported in several observational studies during the precooling period. (1) The phenomenon of MOD is related to the **diving reflex** wherein blood flow to vital organs is conserved at the cost of nonvital organs. The combination of decreased blood flow and hypoxemia can initiate a cascade of physiologic abnormalities that are injurious to multiple organs. Moreover, when MOD occurs, it is likely that the asphyxiated infants with HIE have activated the diving reflex for long enough to result in hypoxic and ischemic injury even to vital organs. (2)(3)

Although the primary focus of the published therapeutic cooling trials was to **reduce the adverse neurodevelopmental outcomes associated with HIE**, a growing awareness of the consequences of the initial hypoxic-ischemic injury on the major organ systems and the resultant complications in the care of asphyxiated infants is now emerging. (4) Because therapeutic hypothermia has become the standard treatment for infants with moderate and severe HIE, clinical management now needs to take into account the effects of therapeutic cooling on the function of the multiple organ systems that have already undergone injury induced by perinatal asphyxia. The impact of cooling on the asphyxia-induced multiple organ dysfunction has been addressed in pilot studies assessing the safety of therapeutic cooling in asphyxiated infants and also in large randomized cooling trials. (5)(6)(7)(8)(9)(10) **The results** of these trials indicate that cooling is usually safe, and, except for **transient thrombocytopenia and sinus bradycardia**, has no other adverse effects on other organs. Nevertheless, these data have been gathered from cooling treatments in the controlled settings of NICUs using strict experimental study guidelines. To obtain an understanding of the morbidities commonly encountered during cooling treatment in non-randomized trial settings, one should refer to various registries (eg, UK TOBY Cooling Register, Baby Cooling Registry of Japan, or The Vermont Oxford Neonatal Encephalopathy Registry). (11)(12)(13) Data from these registries suggest that cooled asphyxiated infants often develop many adverse systemic events, but most of these complications are the result of the asphyxia, and not of the cooling, as shown by the meta-analysis of the published studies.

This review aims to discuss the effect of cooling on neonatal physiology in the current recommended cooling range, because an understanding of the physiologic changes during cooling treatment will be useful in reducing the morbidities related to MOD in asphyxiated infants.

## MORBIDITIES RELATED TO MOD DURING COOLING TREATMENT

### Cardiovascular Morbidities

Cardiac dysfunction is frequently noted after intrapartum hypoxia-ischemia (Table). (14) The laboratory correlation of cardiac muscle injury is **elevation in serum troponin-T** and **the muscle fraction of creatinine kinase**. (15)(16) **Sinus bradycardia and prolongation of the QT interval** on electrocardiography are common occurrences, and **the cardiac output also decreases** linearly with a decrease in temperature during cooling treatment. (17)(18) However, the systemic reviews of the published cooling trials in neonates reveal that the only cardiovascular effect that can be consistently attributed to cooling is sinus bradycardia, with a heart rate **below 80** beats/min, which is clinically benign. (19) Data on “any arrhythmia” was not sufficient, but arrhythmias have been rare despite numerous instances of “overcooling.” (20) The same meta-analysis also showed **no** significant relationship between cooling and hypotension (mean arterial blood pressure <40 mm Hg [8 studies, 1,221 infants; typical risk ratio (RR) 1.0, 95% confidence interval (CI) 0.9–1.0]) or with hypotension needing treatment with inotropic agents (6 studies, 768 infants; typical RR 1.1, 95% CI 0.9–1.2) when comparing cooled and non-cooled infants. (19)

Hemodynamic dysfunction in asphyxiated infants during cooling typically requires continuous cardiorespiratory monitoring, pulse oximetry, and monitoring of blood pressure by the bedside nurse. The nurse should be made aware that cooling is expected to induce changes in the vital sign parameters, especially the heart rate, which necessitates an adjustment of the alarm limits in the cardiorespiratory monitor. (21) Management of hypotension during cooling should follow the same principles of care applied to any asphyxiated infant, regardless of therapeutic cooling. Fluid boluses are to be used judiciously, recognizing that asphyxiated infants can develop fluid overload because of potential complications of syndrome of inappropriate antidiuretic hormone secretion (SIADH) or acute kidney injury (AKI). To treat hypotension, **echocardiography** assessment is suggested to determine the necessity of **fluid boluses** or of **inotropic support** with dobutamine, dopamine, or epinephrine. (20) Management of refractory hypotension may also require hydrocortisone in addition to inotropic support.

### Blood Gases and Ventilation During Therapeutic Cooling

Although most infants are kept intubated during the period of cooling, the positive pressure settings and the fraction of inspired oxygen (F<sub>IO<sub>2</sub></sub>) requirement are usually low while a



TABLE. **Summary of Multiple Organ Dysfunctions in Cooled Infants Collected From Large Therapeutic Cooling Trials**

Reported Adverse Effects During Cooling	CoolCap Study 2005 (8) (N=112)	NICHD Study 2005 (9) (N=102)	TOBY Study 2009 (10) (N=163)	neo.nEURO Study 2010 (49) (N=62)	Zhou 2010 (50) (N=100)	ICE Study 2011 (51) (N=110)
Cardiovascular						
• Cardiac arrhythmia <sup>a</sup>	10 (9)	2 (2)	8 (5)	3 (5)	4 (4)	31 (43)
• Presence of hypotension (MAP <40 mm Hg, or treated with inotropic agents)	62 (55)	42 (42)	126 (77)	33 (53)	NR	51 (46)
Hematologic						
• Thrombocytopenia (platelet counts <150×10 <sup>3</sup> /μL [ $<150 \times 10^9$ /L])	36 (32)	NR	94 (58)	16 (26)	6 (6)	56 (51)
• Coagulopathy resulting in major thrombosis or hemorrhage	NR	3 (3)	NR	3 (5)	3 (3)	3 (3)
Respiratory						
• Presence of PPHN	NR	25 (25)	16 (10)	NR	NR	NR
• Need for inhaled NO	NR	NR	NR	4 (6)	NR	NR
Metabolic						
• Hypoglycemia (blood glucose <2.6 mmol/L)	14 (13)	12 (13)	NR	8 (13)	7 (7)	NR
• Serum potassium <3.5 mmol/L	71 (63)	NR	NR	NR	10 (10)	NR
Culture-confirmed sepsis	3 (3)	5 (5)	20 (12)	7 (11)	NR	6 (6)

Values are n (%). ICE=infant cooling evaluation; MAP=mean arterial pressure; NICHD=National Institute of Child Health and Human Development; NO=nitric oxide; NR=not reported; PPHN=pulmonary hypertension of the newborn.

<sup>a</sup>Almost all cases represent sinus bradycardia with a heart rate below 80 beats/min.

cooled infant is receiving mechanical ventilation. (22) Intubation also **reduces the aspiration risk**, because many asphyxiated infants do **not have a proper gag reflex**. It is desirable to avoid hypocarbia and overventilation during cooling. (20)(23) **Excessive hypocarbia during cooling may alter the autoregulation of cerebral blood flow, reduce cerebral perfusion pressure**, (23) and **lower the threshold for seizures**. (24) Minimum and cumulative Pco<sub>2</sub> less than 35 mm Hg (4.7 kPa) during the early stages of cooling were both shown to be associated with increased risk of death or disability at 18 to 22 months among participants with HIE in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) cooling trial. (23) However, the infants themselves often drive their own ventilation excessively to compensate for metabolic acidosis to the point that it sometimes becomes

difficult to achieve normocapnia. Use of heavy sedation or paralysis has been suggested as a way to establish control over the rate of ventilation and to maintain normocapnia but may not be appropriate. (20) The authors usually perform **extubation** in a cooled infant if hyperventilation persists even after using low ventilator settings. Successful extubation during cooling with no significant clinical signs of aspiration after extubation was possible in almost 40% of the infants. (22)

The **metabolic rate** in an infant usually decreases by approximately **5% to 8% for every 1°C drop in temperature below 37°C**, and results in a **reduction in production of carbon dioxide during cooling**. (25) Blood gas values need to be **corrected** to account for lower body temperature, because Pco<sub>2</sub> and Po<sub>2</sub> decrease by 4% and 7%, respectively, and pH increases by 0.015, for every 1°C drop in core body

temperature. (26) As described in 3 published trials, ventilator adjustments should be based on the corrected blood gas values. (8)(9)(10)

Persistent pulmonary hypertension (PPHN) in infants receiving therapeutic hypothermia has been a concern since Eicher et al reported a higher risk of pulmonary hypertension requiring inhaled nitric oxide treatment during cooling. (7) PPHN was present in 25% of the cooled infants in the NICHD NRN whole-body cooling trial, and was the cause of death in 11% of the cooled infants in the CoolCap trial. (7) However, the risk of PPHN is related more to the underlying cause of the perinatal asphyxia (eg, in utero hypoxia with vascular hypertrophy and remodeling) or may be a response to the ongoing postnatal hypoxemia rather than the cooling. The risk of PPHN (4 studies, 614 infants; typical RR 1.3, 95% CI 0.9–1.9) and the need for inhaled nitric oxide (4 studies, 426 infants; typical RR 1.2, 95% CI 0.7–1.9) or for extracorporeal membrane oxygenation (ECMO) were not different between the cooled and noncooled infants as shown in the systemic review of the cooling trials, (19)(27) and cooling is not contraindicated in asphyxiated infants who already have clinical signs of PPHN. (20) PPHN in a cooling infant usually responds to inhaled nitric oxide treatment, and the need for ECMO is infrequent, as reported previously. (22) In asphyxiated newborns with refractory cardiorespiratory failure, concurrent use of cooling with ECMO is feasible because the desired core body temperature can be maintained within the therapeutic range through the use of the ECMO circuit heat exchanger. (28)

#### Hematologic Abnormalities and Hepatic Dysfunction

Coagulation abnormalities and hepatic dysfunction (elevated levels of alanine aminotransferase or aspartate aminotransferase) are common in asphyxiated infants. (29)(30)(31)(32) Cooling can potentially affect different hematologic parameters, especially **leukocyte function and coagulation**, which may theoretically put the cooled infants at a higher risk of infection and bleeding. However, therapeutic cooling in itself does **not** seem to further worsen coagulopathy or hepatic dysfunction when the target core temperature, as specified in the published cooling protocols, is maintained. A systematic review of the 8 cooling trials also did **not** show any increased risk of sepsis with cooling treatment (1,222 infants; typical RR 0.8, 95% CI 0.6–1.3). (27) The pattern of abnormal liver enzymes among infants with hypoxic-ischemic injury typically follows a course of an **elevation within 6 to 12 hours after birth, with a peak at 48 to 72 hours of age**. (31)(32) Hepatic dysfunction is typically **self-limited**. (14) In both the CoolCap and the NICHD NRN

whole-body cooling trial, around 19% of the cooled infants had coagulopathy. (8)(9) Hepatic dysfunction was present in 38% and 20% of the cooled infants in the CoolCap and the NICHD whole-body cooling trial, respectively. (8)(9) Nonetheless, a systematic review of the published cooling studies showed **no significant adverse effect of cooling on coagulopathy** (7 studies, 1,188 infants; typical RR 1.1, 95% CI 0.9–1.3), or on the incidence of bleeding or major thrombosis arising from coagulopathy (4 studies, 689 infants; typical RR 1.7, 95% CI 0.6–4.8). (19) Cooling also had no statistically significant effect on the presence of hepatic dysfunction (6 studies, 975 infants; typical RR 0.9, 95% CI 0.7–1.05). (19)

Although coagulopathy and hepatic dysfunction are not significantly affected by therapeutic hypothermia, this therapy has been shown to be associated with an increased frequency of transient thrombocytopenia. Systematic review of the cooling trials has consistently shown a significant increase in the incidence of thrombocytopenia, with platelet counts below  $150 \times 10^3/\mu\text{L}$  ( $150 \times 10^9/\text{L}$ ) among the cooled infants (8 studies, 1,392 infants; typical RR 1.2, 95% CI 1.0–1.4); number needed to treat 17, 95% CI 10–50). (19) Fortunately, no increase in bleeding complications has been noted after cooling-associated decrease in platelets. (4)(33) The decrease in platelets after neonatal encephalopathy usually **starts 12 to 24 hours after an insult**, with a **nadir occurring at approximately 48 to 72 hours of age**. (34)

Cooling itself does not alter the clotting or hepatic function, but coagulopathy remains a common occurrence during therapeutic cooling. (14) In the UK TOBY Cooling Registry, coagulopathy requiring intervention was the second most commonly reported morbidity. (11) This highlights the necessity of close monitoring for clotting parameters, liver function, and clinical signs of coagulopathy (eg, oozing from a venipuncture or heelsticks, and/or bloody endotracheal or gastric aspirates) during cooling. Abnormal coagulation studies among infants with severe birth asphyxia have been recognized for almost 50 years. (29) The coagulopathy seen among asphyxiated infants appears to follow a similar time course as the platelet counts, **with initial normal levels soon after birth and subsequent abnormalities at their worst at 48 to 72 hours**. (30) Hyperviscosity and reduced microcirculation stemming from therapeutic cooling could potentially increase the risk for microembolism and disseminated coagulopathy. (20)

Coagulopathy during cooling is usually managed by transfusing fresh frozen plasma, cryoprecipitate, and/or platelets, while following the standard treatment principles applied to any asphyxiated infant. (35) Coagulopathy in asphyxiated infants with subgaleal bleeding after a traumatic

delivery is sometimes difficult to manage and may need to be aggressively treated with frequent administrations of fresh frozen plasma and/or cryoprecipitate, platelets, and packed red blood cells to control ongoing bleeding. (20)

### Renal Dysfunction and Management of Fluid, Electrolytes, and Nutrition During Therapeutic Cooling

AKI is a common coexisting morbidity among asphyxiated infants receiving therapeutic hypothermia. (11)(36)(37)(38) Clinically, AKI is manifested by oliguria or anuria beginning soon after birth, and microscopic hematuria with proteinuria is usually noted during the period of decreased urine output. Typically, serum creatinine levels start rising within hours of birth and peak at 3 to 4 days of age. (39) Assessment of biomarkers of AKI is often suboptimal in the newborn period. Hence, the rate and severity of AKI in cooled asphyxiated infants vary with the criteria used to diagnose AKI in such infants. Using modified Acute Kidney Injury Network criteria based on increases in serum creatinine level compared with a previous trough, the incidence of AKI in cooled asphyxiated newborns was reported to be as high as 38%. (40) Unlike infants without AKI who had decreasing serum creatinine levels throughout the period of cooling, infants with AKI showed a trend toward rising serum creatinine levels during the 72 hours of cooling, as reported in a cohort of 96 consecutively cooled asphyxiated infants. (40) On average, elevated serum creatinine levels persisted in infants with AKI even after cooling until at least 7 days of age, and in some infants, continued to the time of transfer or discharge; however, renal replacement therapy was only deemed necessary in a few rare cases. (40) Glomerular blood flow is usually not affected during cooling, and the rate of acute renal failure or renal impairment of cooled infants did not differ from that of noncooled infants in clinical trials that reported the renal effects of cooling (6 studies, 667 infants; typical RR 0.8, 95% CI 0.7–1.0). (19) Some studies suggested that cooling may be protective to kidneys, (17)(20) and indeed, a trend toward reduced risk of renal impairment with cooling has been found in the Cochrane meta-analysis of the large cooling trials. (19)

Oliguria or anuria and electrolyte abnormalities secondary to AKI may affect the physiologic homeostasis during the cooling treatment. In the whole-body cooling trial, 16% of the cooled infants were oliguric and another 5% were anuric. (9) In one observational study, electrolyte abnormalities were present in more than 50% of infants during cooling, with hyponatremia, hypokalemia, and hypocalcemia being the most prevalent. (14) Cooling may cause an intracellular shift of potassium, resulting in hypokalemia, and severe HIE and infants who had poor outcomes usually

had larger falls in serum calcium levels. (41) However, a systematic review of the cooling trials revealed no statistically significant difference in the rates of hypokalemia (serum potassium <3.5 mEq/L [ $<3.5$  mmol/L]) between cooled and noncooled subjects (5 studies, 738 infants; typical RR 0.9, 95% CI 0.8–1.1). (19) A similar lack of difference in the rates of hypocalcemia between cooled and noncooled groups was also reported in 2 larger cooling studies. (8)(9) It is also important to remember that aggressive correction of hypokalemia during cooling may result in overshoot hyperkalemia at the time of rewarming. (42)

Cooling has been reported to increase glucagon secretion and decrease insulin release and insulin sensitivity in adults and animal models, leading to inappropriately high plasma glucose levels. (43) However, hyperglycemia is very rare during cooling therapy in asphyxiated infants, and therefore, the large cooling trials focused more on the occurrence of hypoglycemia than hyperglycemia. (17) Indeed, a meta-analysis of the cooling studies reported no significant hypoglycemia in the cooled groups (7 studies, 1,030 infants; typical RR 0.8, 95% CI 0.6–1.06). (19)

Management of fluid and electrolytes during cooling treatment involves close monitoring of fluid balance, including monitoring of weight, net fluid intake, respiratory status, and frequent measurements of serum electrolytes and plasma glucose. (35) Fluid restriction is usually necessary because of AKI and the potential complication of SIADH. Fluid and electrolyte levels are adjusted to maintain normal levels of plasma glucose and serum electrolytes during cooling.

In both adult and animal models, cooling has been reported to decrease blood flow to the intestines. (44)(45) Necrotizing enterocolitis and bowel perforation have been reported after cooling, but these complications are extremely rare, and the incidence of necrotizing enterocolitis has been reported to be similar regardless of cooling. (20) Because of concerns about hypoxic-ischemic insult to the intestines, enteral feedings are usually withheld during cooling, similar to the approach in the large cooling trials. (8)(9)

### Drug Metabolism During Therapeutic Cooling

Most of the drugs frequently used in asphyxiated infants during therapeutic cooling, including antibiotics, anticonvulsants, inotropic agents, and sedatives, will potentially have altered metabolism and excretion because of the presence of hypoxic-ischemic hepatic and kidney injuries complicating HIE, as well as because of the cooling therapy. The effects of cooling on the metabolism of drugs commonly used in asphyxiated infants have been reviewed. (46)

Cooling therapy slows the kinetics of most of the enzymatic pathways in drug metabolism. Biotransformation of a medication, usually by the cytochrome P450 enzyme system in the liver (phase 1 metabolism), and enzymatic conjugation of a medication with other molecules (phase 2 metabolism) to facilitate excretion via the kidneys or the intestines are most affected by cooling. (46) Drugs that are eliminated unchanged largely through the kidneys (phase 3) are unlikely to be affected by cooling treatment.

The drugs most commonly used during cooling that undergo phase 1 metabolism include anticonvulsants (eg, phenobarbital, phenytoin, and carbamazepine); agents used for sedation (eg, fentanyl and midazolam); neuromuscular paralyzing agents (eg, vecuronium); and corticosteroids. (46) The metabolism of these drugs is slowed, causing an accumulation of these drugs during cooling. The half-life of phenobarbital has been reported to double in cooled asphyxiated infants compared with noncooled controls. (46) Clearance of phenytoin was also noted to decrease by 67% when adults with traumatic brain injury were cooled to 34°C. (47) Unlike fentanyl, morphine is mostly metabolized by enzymatic conjugation (phase 2 metabolism). Reduced metabolism of morphine during cooling has been shown to decrease clearance of morphine by approximately 22% and increase the serum morphine levels by 42% in asphyxiated infants. (47) Hence, it is important to closely monitor the levels of seizure medications administered during treatment of seizures, and closely assess the level of sedation while sedation and analgesia are being used during cooling.

Antibiotics (eg, gentamicin for presumed sepsis) and inotropes (eg, dopamine, dobutamine, or epinephrine for hypotension) are also commonly administered to sick infants with HIE. Cooling does not affect serum levels of gentamicin, (48) because it is eliminated unchanged mostly through the kidneys (phase 3). However, trough serum concentrations of amnioglycosides must be measured to determine whether dose adjustments are needed in neonates with renal dysfunction, which is common in asphyxiated infants who are receiving cooling treatment. Inotropes are mostly metabolized by the monoamine oxidase and catechol-O-methyl transferase pathways; to date, researchers have found no significant differences in response to inotropic support between cooled and noncooled infants. (20)

## CONCLUSIONS

The effects of a perinatal hypoxic-ischemic insult on multiple organ systems were generally acknowledged even before therapeutic cooling became the standard protocol

for moderate and severe cases of HIE. Every physiologic process in an asphyxiated infant can potentially be affected by therapeutic hypothermia. However, the most recent meta-analyses of the collective body of cooling trials suggest that apart from thrombocytopenia and sinus bradycardia, therapeutic cooling (in the current recommended cooling range) in itself does not meaningfully affect the rate or the severity of multiple organ system complications commonly present in asphyxiated infants who received cooling compared with those who did not. Infants with multiple organ system dysfunction during cooling should be closely monitored. Effective management requires intensive care support along with readily available subspecialty consultants, trained multidisciplinary staff, and adequately effective diagnostics, all using the same standards of treatment as for any asphyxiated infant, whether receiving cooling or not. Because therapeutic cooling is now the standard of care, centers that provide cooling treatment should participate in the national benchmarking of short-term outcomes and adverse events to facilitate local quality improvement efforts.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the neonatal systemic complications and vascular redistribution of blood flow caused by perinatal hypoxia or asphyxia.

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# Multiple Organ Dysfunction During Therapeutic Cooling of Asphyxiated Infants

Indira Bhagat and Subrata Sarkar

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## Fetal Head Compression

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During labor, external forces are exerted on the fetal head by uterine contractions and maternal pushing. The exact effect of the external forces on the intracranial pressure, fetal brain, and cerebral blood flow are not known. The reason for this lack of information is the difficulty studying the effect of external forces in human neonates with our current technology. However, several studies have been published that give us insight into the effect of these forces on the fetal head and brain during labor. These studies will be briefly reviewed. Please note that more extensive reviews are also available on the subject. (1)

Several studies have examined the pressure applied to the fetal head during labor and maternal pushing using pressure sensors placed alongside the fetal head. Most studies have indicated that the peak pressure between the fetal head and the pelvis may be as high as 120 to 300 mm Hg during normal labor. (1)(2)(3)(4)(5) A single study reported pressures outside the previous reported ranges, with pressures ranging from 235 to 514 mm Hg. (6) It should be noted that the highest pressures reported in all of these studies occur at the largest diameter of the skull and are lower in other regions. (1)

The fetal head has unfused sutures and is able to deform in shape. Because of these adaptations, one wonders if the external pressures placed on the fetal skull are transmitted to the intracranial space, resulting in an increase in intracranial pressure? Studies performed that directly measured intracranial pressures in neonates with lethal hydrocephalus demonstrated that the intracranial pressure remained quite stable while high external forces were placed on the skull during contractions. (7,8) These studies evaluated the intracranial pressure by measuring a baseline value for the intracranial pressure and subtracting the intra-amniotic pressures. (1) This step was undertaken to control for pressures placed exclusively on the head during contractions. Caution should be used in interpreting these results to healthy neonates because all of the neonates studied had congenital hydrocephalus.

Cerebral oximetry has been used to understand the changes in cerebral oxygenation with contractions and compression of the head. Aldrich et al studied 30 healthy pregnant women with uncomplicated labor. (9) They inserted a specially designed fetal optical probe through the dilated cervix and applied it against the side of the fetal head. (9) Cardiotocography was used to simultaneously monitor fetal heart rate and uterine contractions. (9) In fetuses with no significant change in the fetal heart rate or a change in baseline of less than 15 beats/min, the measured oxyhemoglobin and deoxyhemoglobin fell in parallel. (9) The authors concluded that this parallel drop represented a mechanical expulsion of blood from the cranial cavity and they did not observe a drop in the oxygenation. (9) In contrast, variable fetal heart rate decelerations were associated with a significant decrease in cerebral oxygenation, which occurred immediately after the uterine contraction.

### EDITOR'S NOTE

The Legal Briefs in the July 2019 issue of *NeoReviews* focuses on the topic of fetal head compression. Several readers wanted to learn more about our current knowledge about this topic. Thus, we asked Dr Weiss, a neonatologist with a particular interest in neonatal brain injury, to summarize the evidence behind our current understanding of fetal head compression during labor and how this compression affects the fetal brain.

**AUTHOR DISCLOSURE** Dr Weiss has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

(9) Umbilical cord compression produces variable decelerations, and the compression leads to an interruption in the delivery of oxygenated blood from the umbilical vein to the fetus. Taken together, these data suggest that cerebral oxygenation tracks systemic oxygenation during labor. (1,9) Cerebral oximetry has also been used to understand the effect of contractions on intracerebral blood volumes. During the second stage of labor, cerebral blood volumes have been shown to have a significant increase in the mean cerebral blood volume. (10)

Fetal electroencephalography (EEG) has been used to study the functional significance of contractions on fetal brain activity in 25 primigravida women. (11) Fetal head compression was confirmed on clinical examination as assessed by severe head molding. There was no significant difference in the quantity of fetal EEG abnormalities in the groups with marked head compression compared to the groups without marked head compression. (11) Deterioration in the fetal EEG to a flat background was associated with the development of acidemia. (11) Based on these data, the authors concluded that there was no significant deleterious change in the fetal EEG as a result of head compression, unless fetal acidemia supervened. (11)

Animal models have also been used in an attempt to understand the effect of contractions on the fetal cerebral blood flow. (12,13) In fetal sheep, intracranial pressure was slowly increased in increments of 6 mm Hg by infusion of artificial cerebral fluid into the lateral ventricles via a surgically placed catheter. (13) When the intracranial pressure was raised to within 28 mm Hg of the baseline mean arterial blood pressure, arterial pressures began to rise. (13) Cerebral blood flow and oxygen uptake at the highest intracranial pressures did not change from baseline values. (13) The arterial plasma concentrations of epinephrine, norepinephrine, and arginine vasopressin increased following the increase in intracranial pressure. (13) The renal, gastrointestinal, and skin perfusion decreased by 68%, 69%, and 65%, respectively, at the highest intracranial pressures. (13) The authors concluded that fetal sheep had a highly developed Cushing response, which may play a role in ensuring cerebral viability when the fetal head is compressed during labor. (13)

As this brief review demonstrates, the effect of contractions on the fetal head does not appear to produce significant intracranial pressures, decreases in cerebral blood flow, or changes in fetal EEG. When compression is accompanied by systemic desaturations and acidemia, cerebral oxygenation decreases and fetal EEG changes. An analogy proposed by Dr Heyborne in his review summarizes our current understanding of isolated fetal head compression, how the immense force on the head is tolerated by the fetal

skull with unfused sutures, and how it results in minimal increases in intracranial pressure, while maintaining cerebral oxygenation and perfusion (1):

*"Imagine a car raised on a lift and the tires inflated to 35 psi [pounds per square inch]. When the car is lowered to the ground, the entire weight of the car is placed on the tires. The flexible tires (analogous to the fetal head) change shape (molding) against the hard floor (bony pelvis) with the tires now supporting the entire 4,000-lb weight of the car (contractions or pushing), yet the tire pressure (intracranial pressure) does not change (maintaining cerebral perfusion and oxygenation in the fetus)."*

In conclusion, the body of literature on this topic is very limited and is a ripe area for future investigation.

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# Index of Suspicion in the Nursery

## 1 An Enigma of Recurrent Extubation Failure in a Neonate

Ayesha Romana, MD,\* Indhuja Rajarathinam, MD,\* Prathik Bandiya, DM,\*  
Rajendra Shinde, MD,\* Niranjan Shivanna, MD,\* Naveen Benakappa, MD\*

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### PRESENTATION

A 10-day-old male neonate is referred in view of inability to wean off respiratory support. The infant is born through assisted breech delivery with a birthweight of 2.75 kg to a gravida 2 woman. Antenatal history is not significant. However, there is meconium staining of the amniotic fluid. The infant did not cry after birth and his Apgar scores are 3 and 6 at 1 minute and 5 minutes, respectively. He has cyanosis and tachypnea soon after birth requiring intubation. Vital signs at admission include a temperature of 97.7°F (36.5°C), heart rate of 155 beats/min, capillary refill time of 2 seconds, and saturation of 94% on ventilator. The infant's activity is diminished, with poor tone in all 4 limbs.

The possibilities considered at this stage are perinatal asphyxia, meconium aspiration syndrome, congenital pneumonia, congenital heart disease, sepsis, and persistent pulmonary hypertension of the newborn.

Initial investigations indicate negative sepsis screen (total white blood cell count 20,000/ $\mu$ L [ $20 \times 10^9$ /L], C-reactive protein <6 mg/L [57.1 nmol/L], absolute neutrophil count 15,800/ $\mu$ L [ $15.8 \times 10^9$ /L]); normal blood glucose (98 mg/dL [5.4 mmol/L]); hemoglobin 10.7 g/dL (107 g/L); ionized calcium 4.8 mg/dL [1.2 mmol/L]; and normal blood gas analysis (pH 7.37,  $P_{CO_2}$  39 mm Hg [5.2 kPa],  $P_{O_2}$  73 mm Hg [9.7 kPa], bicarbonate 22 mEq/L [22 mmol/L]). Chest radiography shows normal lung fields bilaterally with fracture of right clavicle (Fig 1).

**NOTE** The editors and staff of NeoReviews find themselves in the fortunate position of having too many submissions for the Index of Suspicion in the Nursery column. Our available publication slots for the column are filled, and because we do not think it is fair to delay publication unduly, we have decided not to accept new cases for the present. We will make an announcement in NeoReviews when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors and to publish only timely medical information. We are grateful for your interest in the journal.

**AUTHOR DISCLOSURE** Drs Romana, Rajarathinam, Bandiya, Shinde, Shivanna, and Benakappa have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Radiograph showing normal position of diaphragm (on ventilator).

## CASE PROGRESSION

The infant is maintaining saturation with minimal pressures on synchronized intermittent positive pressure ventilation, and hence extubation is planned. He has minimal spontaneous respiratory efforts (respiratory rate 20 breaths/min) and develops cyanosis and bradycardia within minutes of extubation, leading to reintubation. However, there is no increase in pressure and oxygen requirement. Bronchoscopy performed to rule out congenital malformations of the airway and lung has a normal result. A trial of extubation is considered, which failed twice in an interval of 48 hours.

At this stage, it is decided to again review the history and clinical examination findings to ascertain the cause for recurrent extubation failure. Characteristic posture noted in the upper limbs was adduction, internal rotation of arm with pronation, and extension at elbow joint. This was suggestive of Erb palsy. There is no movement of the upper limbs with hypotonia, power of 1/5 (grading on the Medical Research Council Scale for Muscle Strength), and absent biceps and triceps jerk. On the contrary, posture, tone, power, and reflexes are normal in the lower limbs. Also, the infant has normal sensorium. Repeat chest radiography at this stage reveals elevated bilateral diaphragms, more on the right side. In the background of difficult delivery, this correlates with birth injury, leading to phrenic nerve injury and bilateral diaphragmatic palsy. (Fig 2) Magnetic resonance imaging and



Figure 2. Radiograph showing elevated right hemidiaphragm (after tracheostomy).



Figure 3. Magnetic resonance imaging scan showing injury to spinal cord.

computed tomography of the spine reveal C3-C5 root avulsion injury leading to pseudomeningocele (Figs 3–5). In view of prolonged respiratory support, tracheostomy is planned.



Figure 4. Magnetic resonance imaging scan showing injury to spinal cord.

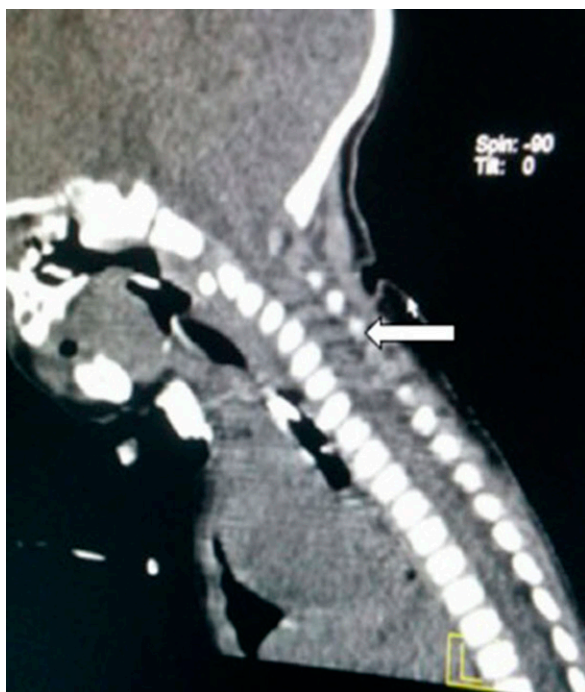


Figure 5. Computed tomography scan showing cervical injury.

Diaphragmatic plication is done on the right side. He undergoes ventilation for a period of approximately 45 days. During this course, he develops spontaneous movements of the left upper limb, with the power increased to 3/5, with no improvement on the right side. The infant is weaned to continuous positive airway pressure (CPAP) 5 days after surgery and then to room air. He is discharged at 3 1/2 months of age. At the time of discharge, he is active, alert, accepting feeds well, and gaining weight with minimal distress.

## DISCUSSION

Birth injuries are a diverse set of conditions occurring in a neonate because of a traumatic event during the process of delivery. (1) Diaphragmatic palsy resulting from phrenic nerve injury is a relatively uncommon form of birth injury, but nearly 80% to 90% of cases have associated brachial plexus injury. (2) Isolated diaphragmatic palsy is uncommon, with a prevalence of about 0.14 per 1,000 live births. (3)

Apart from birth injury, other common etiologies include iatrogenic (cardiothoracic surgery, invasive cannulation) and neuromuscular disorders. Injury to the phrenic nerve during cardiovascular surgery is the most common cause followed by birth injury. (4)

Injury to the phrenic nerve and spinal cord occurs because of excessive traction placed on the spine during delivery of the shoulder in a cephalic presentation and delivery of the head in a breech presentation. (2) The risk of injury is higher during the neonatal period because of ligament laxity, weak musculature, and incomplete mineralization of the vertebrae. (3)

Diaphragmatic palsy following birth injury is most commonly unilateral (right>left). Bilateral involvement, which occurs in less than 10% of cases, is seen in neonates with severe birth injury. (5)(6) In the current case, the birth injury was severe enough to cause bilateral diaphragmatic palsy.

Diaphragmatic palsy should be suspected when there are recurrent failed extubation attempts in the background of a traumatic delivery, especially with breech presentation. Affected neonates can have decreased chest movement on the affected side, with corresponding increased movement on the unaffected side and paradoxical chest movement. (7)

Because most of these neonates receive positive pressure ventilation, clinical and radiologic findings can be easily obscured, as in our case. Elevated hemidiaphragm, which is usually seen in these cases, may not be present if the neonate is receiving positive pressure ventilation. (2) Ultrasonography is the preferred method because it is safe, does not carry any risk of radiation exposure, and can be done serially to assess the diaphragmatic function. (8)

Management includes supportive care in the form of supplemental oxygen, nasal CPAP, and mechanical ventilation depending on the severity. CPAP has been shown to be beneficial in some patients and a trial should be given in every neonate because it avoids intubation. (2)

Surgical intervention should be considered usually after 1 to 2 months of positive pressure ventilation when there is no recovery. (2) Surgical plication of the affected diaphragm is the commonly performed procedure and a satisfactory response is seen in most cases. (9)

Phrenic nerve stimulation may help in making a decision regarding surgery, with prolonged conduction latencies or reduction in amplitude or absence of diaphragmatic action potentials indicating poor chances of spontaneous recovery. (10)

In the current case, the main presentation was recurrent extubation failures with minimal ventilator settings and normal sensorium. This infant also had bilateral Erb palsy, which led us to evaluate for associated phrenic nerve injury because of the spinal cord trauma leading to diaphragmatic palsy.

### Lessons for the Clinician

- Diaphragmatic palsy should be considered in neonates in cases of recurrent extubation failures, especially if it is associated with a history of abnormal presentation or traumatic delivery.
- All cases of Erb palsy with respiratory distress or extubation failures should be evaluated for associated phrenic nerve injury.
- Clinical and radiologic signs of diaphragmatic palsy can be missed in a neonate receiving positive pressure ventilation.
- Imaging of the spine is recommended to rule out other associated injuries.

### American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical features and prognosis of birth injuries, such as fractures, lacerations, and facial palsies.

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# Index of Suspicion in the Nursery

## 2 Chronic Testicular Torsion in a Healthy Neonate

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### PRESENTATION

A male newborn, weighing 3,180 g, is born via spontaneous vaginal delivery at 38 3/7 weeks' gestation to a 26-year-old, gravida 4, para 3 woman. The pregnancy is uncomplicated and the family history negative. At birth, the right scrotum is swollen and the left testis is not palpable. Scrotal ultrasonography shows a right hydrocele with mild swelling and reduced perfusion of the right testicle (Fig 1A and 1B). The left testicle appears to be in the left inguinal canal with blood flow present (Fig 2A and 2B). He is discharged on day 2 with outpatient follow-up scheduled with urology in 1 week.

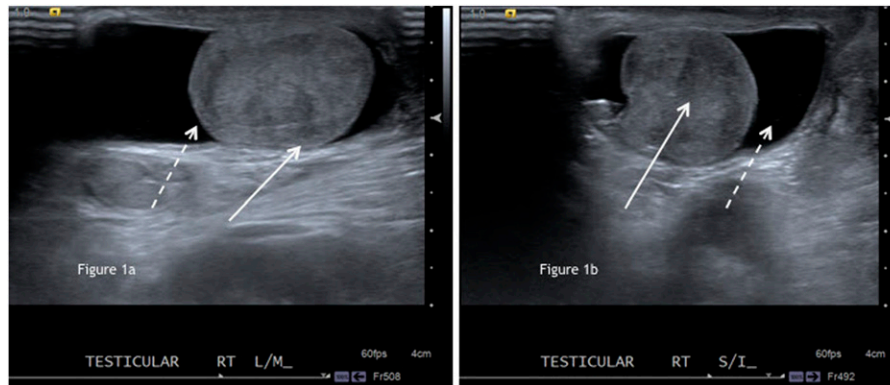
The family does not follow up, and the infant presents at 4 weeks of age with bilateral testicular swelling. On examination, the left testis is not palpable and there is diffuse scrotal swelling with no surrounding erythema. Cremasteric reflex is present on the right, but absent on the left. No chordee is noted and transillumination of scrotal skin is negative. Hypertrophy of the right leg is noted, which had been missed on initial examination. The maximum circumference of the right thigh is 16.0 cm compared with 14.0 cm on the left. Hormonal assays including follicle-stimulating hormone, luteinizing hormone, and total testosterone levels are normal. Venous duplex ultrasonography of both lower extremities is negative. Ultrasonography of the abdomen reveals no masses, though there is an incidental grade 1 to 2 dilation of the right renal collecting system. Repeat ultrasonography of the scrotum 29 days later shows perfusion of both testicles with heterogeneity and coarse echotexture (Fig 3A and 3B). Scrotal exploration, right testicular biopsy, and bilateral orchiopexy are performed.

Interestingly no twisting of spermatic cords is noted. Viable seminiferous tubules are noted on initial frozen pathology and histologic examination confirms atrophic and hemorrhagic necrosis of the right testicle consistent with chronic torsion with no evidence of neoplasm.

### DISCUSSION

Testicular torsion is twisting of the spermatic cord strictures and subsequent loss of blood supply to the ipsilateral testicles, leading to a surgical emergency. Testicular torsion can be extravaginal or intravaginal. Extravaginal torsion is more common in newborns and involves torsion of the tunica vaginalis and investing outer layers. The weak anchoring between the tunica vaginalis and scrotal wall allows the tunica vaginalis and its contents to rotate around the axis of the spermatic cord. Intravaginal torsion is more common in older children and involves twisting of the testis within the tunica vaginalis.

**AUTHOR DISCLOSURE** Drs Salman and Goyal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



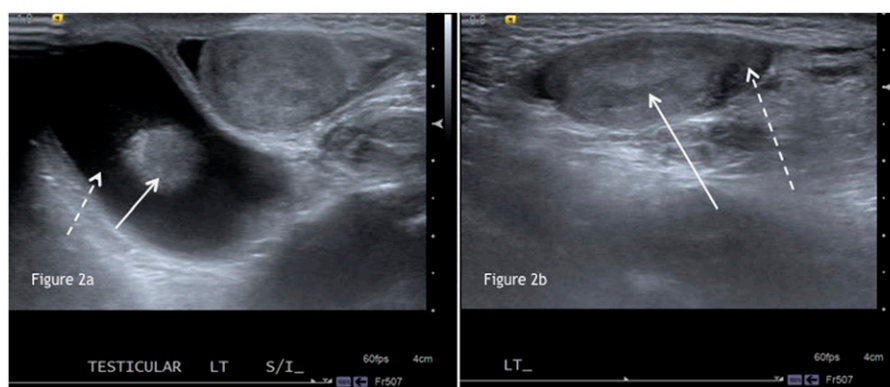
**Figure 1.** Sagittal views of the right testicle demonstrate course, heterogeneous echotexture and a moderate-sized hydrocele and no focal mass.

Most neonatal torsions are unilateral and only a few cases of bilateral torsion have been described. Seventy percent of unilateral neonatal testicular torsions present within a few hours of birth and 30% present within the first 30 days. Our patient presented after 30 days with appropriate weight gain. He had an abnormal testicular examination and was found to have heterogeneous appearance of bilateral testicles on scrotal ultrasonography, which led to the possibility of a neonatal torsion event. Upon surgical exploration and histologic evaluation, chronic bilateral testicular torsion was diagnosed. Frozen pathology results revealed viable seminiferous tubules with necrosis, which is not consistent with straightforward neonatal testicular torsion. In a typical testicular torsion event, twisting of the spermatic cords causes vascular compromise, leading to ischemia and if not corrected, can result in necrosis and testicular nonviability. Our patient had no twisting of the spermatic cords and normal Doppler flow was noted on ultrasonography, yet a testicular torsion was diagnosed based on histologic results. It is possible there may have been a compromise in testicular vascular flow with restoration of flow in utero, resulting in viable seminiferous

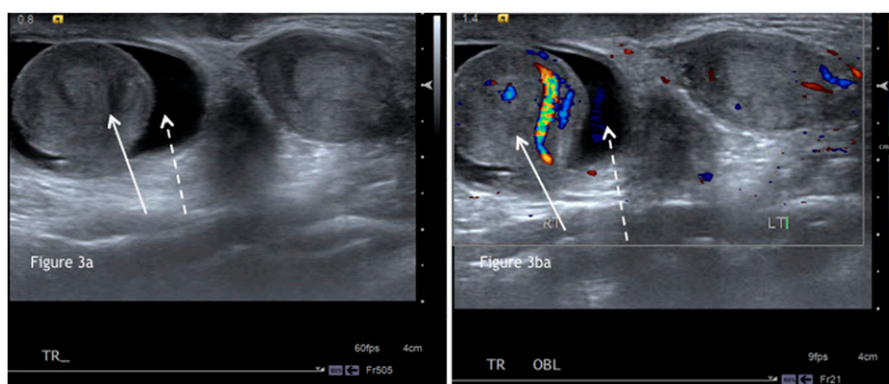
tubules with tissue necrosis. Nevertheless, it is essential to rely on a thorough physical examination to reach the diagnosis and surgical intervention should take place if a diagnosis is in doubt.

The possibility of testicular torsions in healthy neonates is rare, but should be considered. Testicular torsion can cause acute ischemia, hemorrhage, and necrosis, resulting in abnormality of testicular function and infertility. Studies of testicular torsion in older children have shown that about 12 hours of ischemia is sufficient to produce permanent damage to the Leydig cells and compromise of testosterone production. Our case was unique in that our patient did not have a decline in hormonal function despite having torsion 33 days after birth, which was presumably present for days or weeks.

Our patient also had right leg hemihypertrophy. Hemihypertrophy is referred to as hemihyperplasia involving abnormal growth of cells in one or more body parts. Infants with isolated hypertrophy have been noted to have an increased risk for developing embryonal tumors especially Wilms tumor and hepatoblastoma. Abdominal and venous ultrasonography did not reveal any tumors. Genetic



**Figure 2.** These transverse and sagittal images of the left testicle demonstrate coarse heterogeneous echotexture with a trace hydrocele and no focal mass.



**Figure 3.** These images demonstrate the bilateral testes in the transverse plane. Again, there is a heterogeneous, coarse echotexture of testis bilaterally. The Doppler image shows flow present within both testicles.

evaluation is planned, however, the family has not followed up for evaluation.

### Conclusion

Neonatal testicular torsion is a surgical emergency occurring within the first few hours after birth and is associated with a poor prognosis. Rare cases of bilateral testicular torsion with normal growth and development have been described. We report a unique case of chronic testicular torsion in a healthy neonate with an incidental finding of right leg hypertrophy. Clinical diagnosis of testicular torsion in neonates can be a challenging task because most cases are asymptomatic; therefore, it is important to perform a detailed testicular physical examination and use ultrasonography as an adjunct for diagnosis. Although rare, testicular torsion should be considered in the differential diagnosis of a thriving neonate who presents with swollen testes.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the neonatal complications of abnormal presentations (breech, shoulder dystocia, etc).

## Suggested Readings

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## Laboring the High-Risk Gestation

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by  $>25$  beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of  $<110$  beats/min; tachycardia is a baseline of  $>160$  beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of  $\geq 2$  cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute

**AUTHOR DISCLOSURE** Drs Demasio and Ryken have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



TABLE 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695.

#### • Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline

–Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period

–Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

#### INTERPRETATION

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation

- Recurrent variable decelerations with minimal or moderate variability
- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106.* Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## THE CASE

A 29-year-old gravida 6, para 2-3-0-2 woman arrived at the labor and delivery (L&D) department at 39-0/7 weeks

of gestation for a scheduled induction of labor. The indication for labor induction was a prior history of intrauterine fetal death. The prenatal course in this pregnancy began at 7 weeks' gestation with a maternal-fetal medicine subspecialist because of an inadequate obstetric history. The woman's first pregnancy was delivered by cesarean in the Middle East at 39 weeks of gestation. She reported a failure to progress in the first stage of labor that led to an uncomplicated cesarean delivery. The operative report for this delivery was not available, but she desired a trial of labor. Three years after her first delivery, her second child was born via a successful vaginal birth after cesarean (VBAC) that was also at 39 weeks of gestation. The third and fourth pregnancies unfortunately ended with intrauterine fetal deaths at 26 and 28 weeks of gestation, respectively; both of these deliveries were vaginal. Another pregnancy was complicated by antenatal diagnosis of mosaic trisomy 18 that was surgically terminated at 23 weeks of gestation. The patient reported that she and her husband were first cousins, so they received genetic counseling, carrier screening, and opted for chorionic villus sampling that revealed a normal karyotype in the current pregnancy. Other than class I obesity, with a body mass index of 32 kg/m<sup>2</sup>, the remainder of the medical history was uncomplicated or noncontributory. Her only medications were prenatal vitamins and occasional antacids for pregnancy-related reflux. Because of her history of fetal death, antepartum surveillance was initiated early in the third trimester, and the FHR tracing obtained a day before her induction of labor was reactive (Fig 1) and representative of her reassuring outpatient nonstress test.

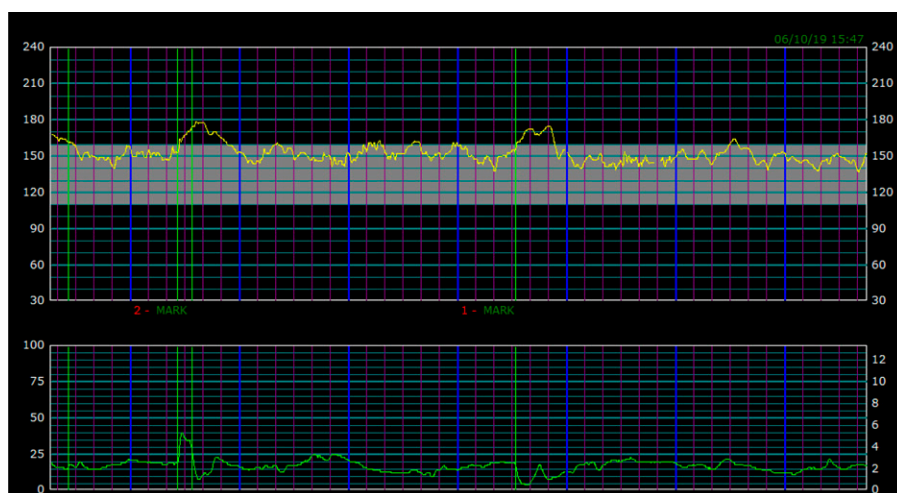


Figure 1. Electronic fetal monitoring strip 1.

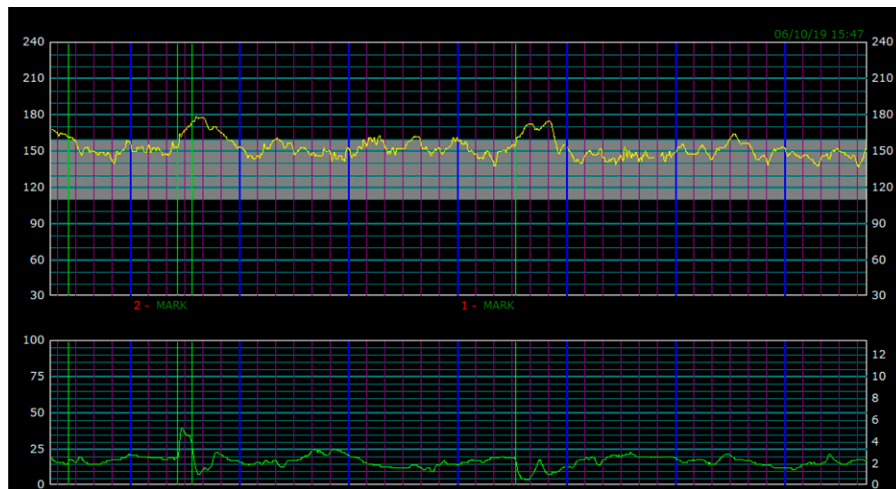


Figure 1. Electronic fetal monitoring strip 1.

Findings in EFM strip 1 are as follows (Fig 1).

- Baseline rate: 150 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: No contractions
- Interpretation: Reactive or category I
- Differential diagnosis: Reactive and reassuring FHR
- Action: None

Upon admission to L&D, her vital signs were normal and an examination of the cervix revealed a long, closed, and posterior cervix. All laboratory values were appropriate and the estimated fetal weight was 3,500 g. Before the use of induction agents or medications, the index FHR tracing during her admission revealed a spontaneous prolonged deceleration (Fig 2), which delayed the start of the induction process so that the FHR tracing could be further observed.

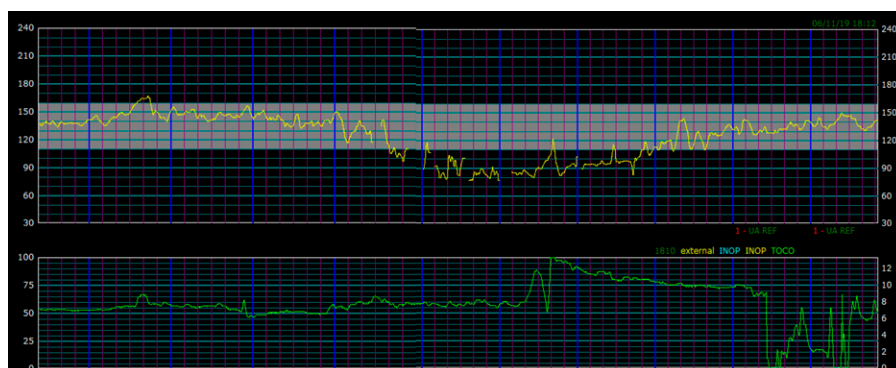


Figure 2. Electronic fetal monitoring strip 2.

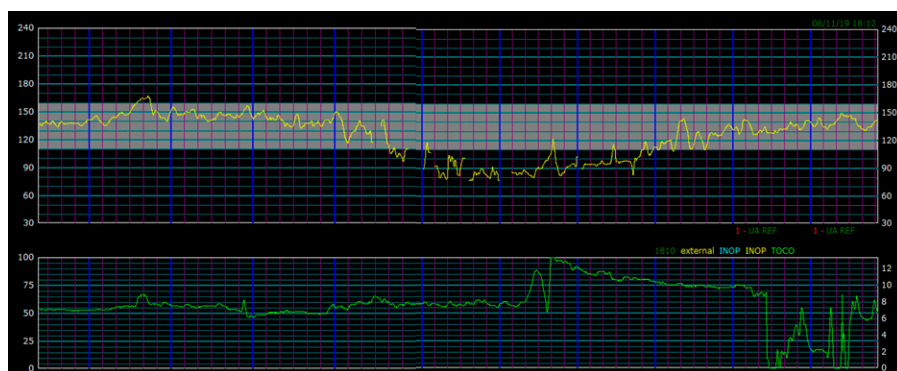


Figure 2. Electronic fetal monitoring strip 2.

Findings in EFM strip 2 are as follows (Fig 2).

- Baseline rate: 145 beats/min
- Baseline variability: Moderate
- Episodic patterns: Prolonged deceleration
- Periodic patterns: None
- Uterine contractions: Not clearly observed on monitor
- Interpretation: Category II tracing
- Differential diagnosis: Umbilical cord compression
- Action: Maternal position change, adjustment of external tocometer, and oxygen by face mask

The tracing soon became a category I (Fig 3) and labor induction was started with oxytocin.

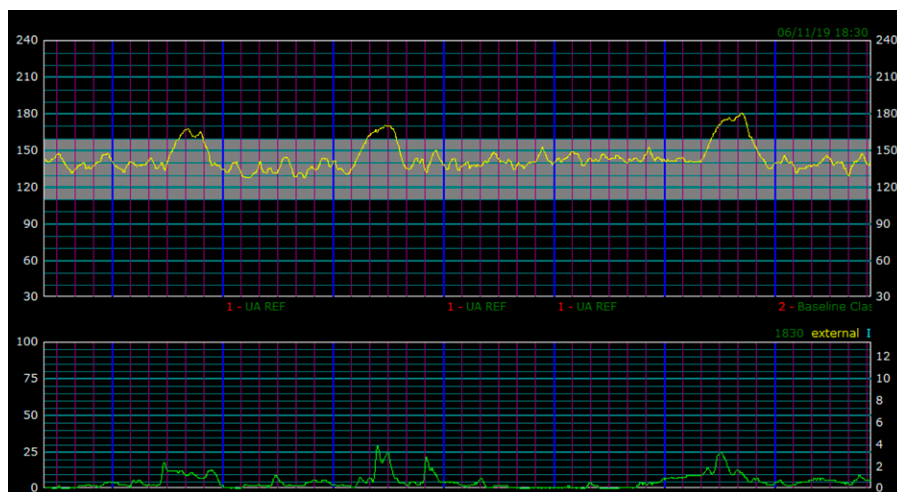


Figure 3. Electronic fetal monitoring strip 3.

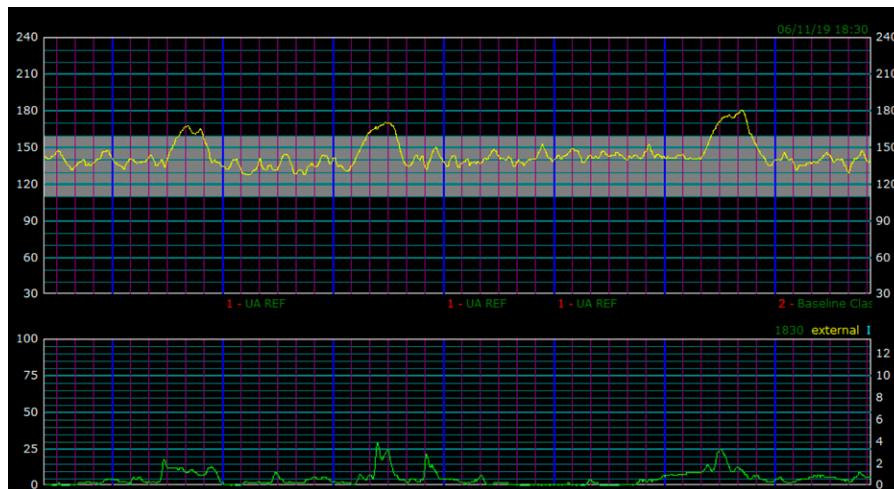


Figure 3. Electronic fetal monitoring strip 3.

Findings in EFM strip 3 are as follows (Fig 3).

- Baseline rate: 140 beats/min
- Baseline variability: Moderate
- Episodic patterns: Accelerations without decelerations
- Periodic patterns: None
- Uterine contractions: Not clearly observed on monitor
- Interpretation: Category I tracing
- Differential diagnosis: Reactive and well-oxygenated fetus
- Action: None

She requested epidural analgesia 3 hours after the start of the induction, at which time, her cervix was 3-cm dilated, 20% effaced, and the vertex was at  $-3$  station, so a combined spinal epidural analgesia was placed. Membranes were artificially ruptured after another 6 hours and clear amniotic fluid was observed. The cervical examination progressed to 6-cm dilation, 50% effacement, and station remained at  $-3$ . The FHR tracing shown in Fig 4 indicated an active labor pattern as regular uterine contractions were present every 2 minutes.

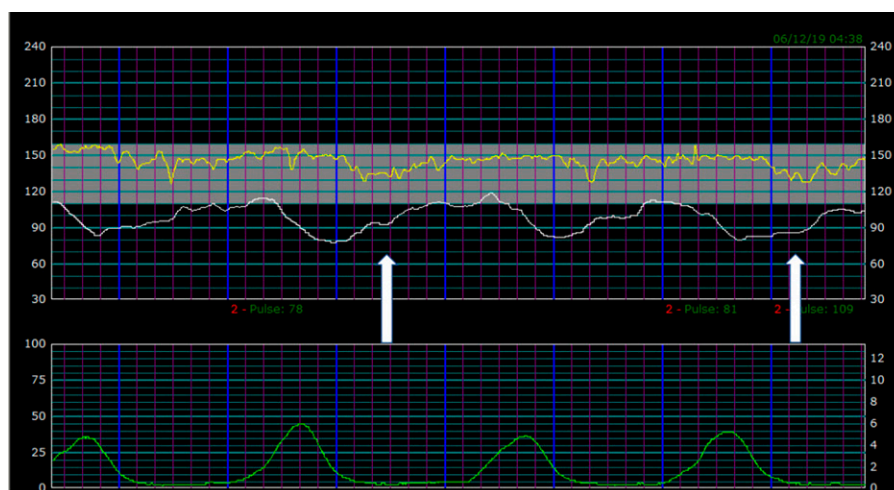


Figure 4. Electronic fetal monitoring strip 4.



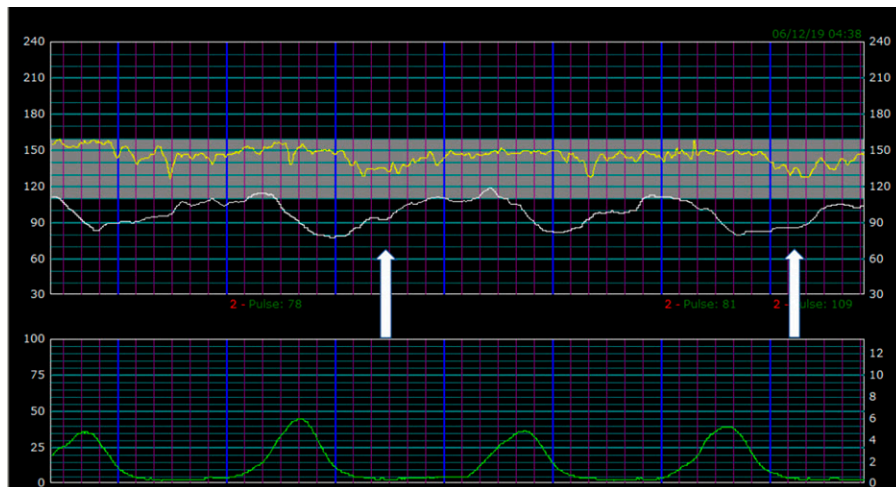


Figure 4. Electronic fetal monitoring strip 4.

Findings in EFM strip 4 are as follows (Fig 4).

- Baseline rate: 150 beats/min
- Baseline variability: Moderate
- Episodic patterns: None
- Periodic patterns: Late decelerations (arrows)
- Uterine contractions: Every 2 min
- Interpretation: Category II tracing
- Differential diagnosis: Caution for the development of placental insufficiency
- Action: Intravenous fluid bolus to increase uterine perfusion, maternal position change, oxygen by face mask; intrauterine resuscitation.

Also present on the FHR tracing (Fig 4) were subtle late decelerations (white arrows) after some of the contractions even though the baseline heart rate maintained moderate variability. After an hour, she was completely dilated to 10 cm and the vertex now was at 0 station, however the presentation was assessed to be occiput transverse. Given that she was multiparous and believed to have an adequate pelvis, she began pushing in her second stage of labor. The FHR tracing soon changed (Fig 5) and recurrent decelerations were present.

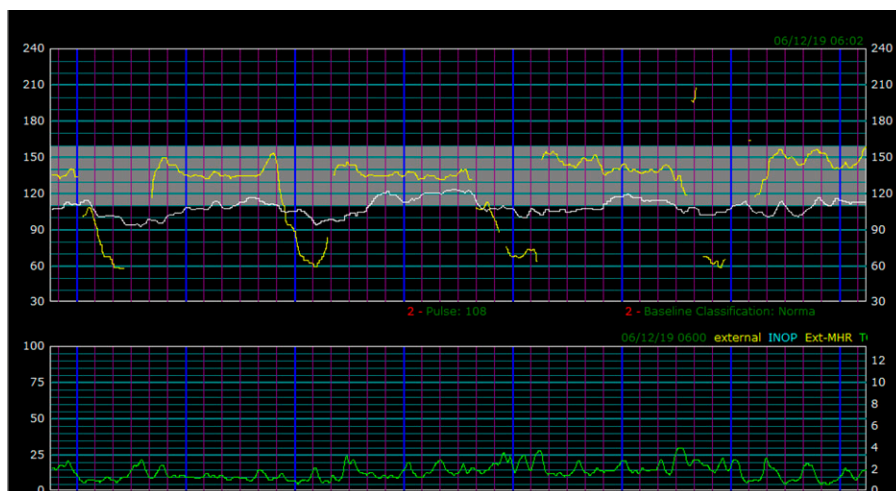


Figure 5. Electronic fetal monitoring strip 5.



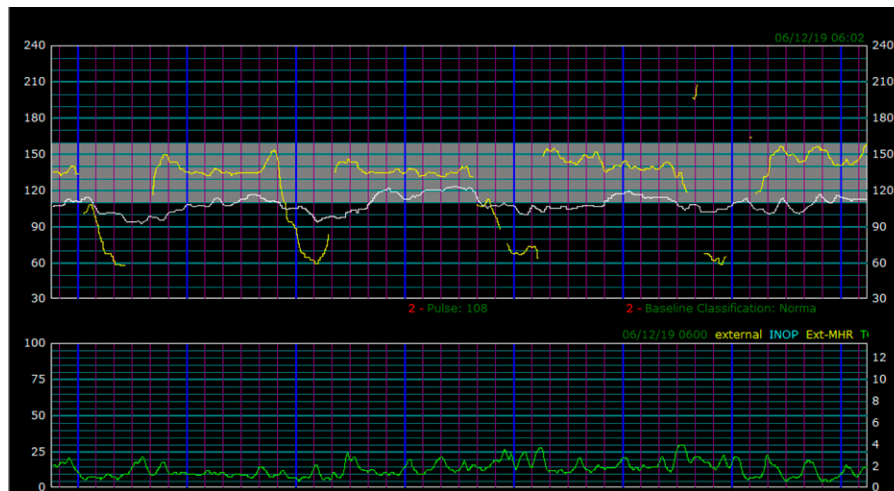


Figure 5. Electronic fetal monitoring strip 5.

Findings in EFM strip 5 are as follows (Fig 5).

- Baseline rate: 135 beats/min
- Baseline variability: Moderate
- Episodic patterns: Recurrent variable decelerations
- Periodic patterns: None
- Uterine contractions: Not present; tocometer appears to have “uterine irritability”
- Interpretation: Category II tracing
- Differential diagnosis: Umbilical cord compression, nuchal cord, and uterine rupture
- Action: Intrauterine resuscitation, restore monitoring of contractions, determine likelihood of vaginal delivery

No internal monitors, such as an intrauterine pressure catheter or fetal scalp electrode, were used during the labor process, so the FHR tracing was discontinuous and the contraction pattern became absent. The vertex descended to +2 station, but remained transverse. She pushed for a total of 2 hours with good maternal effort but no descent occurred and a transverse arrest was diagnosed. The clinicians did not recommend operative vaginal delivery because of the transverse presentation but rather advised for a repeat cesarean, which was accepted by the patient. The FHR tracing just before the repeat cesarean as shown in Fig 6, was a concerning category III tracing because of absent variability and recurrent decelerations.

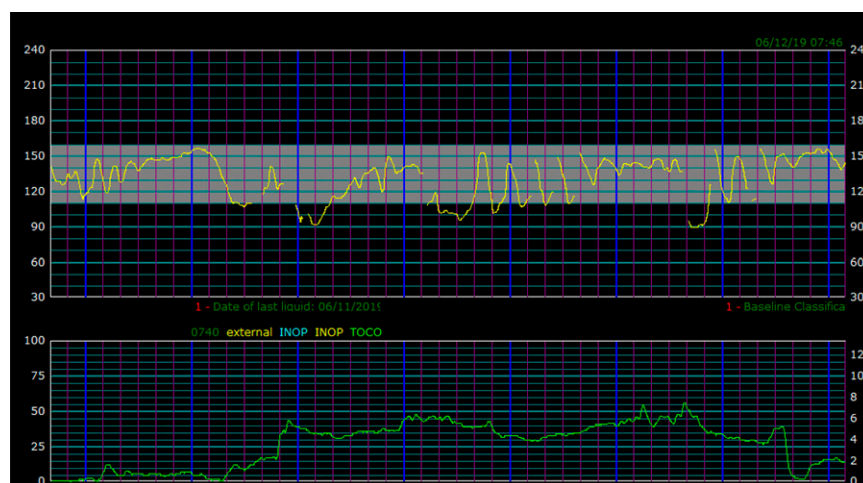


Figure 6. Electronic fetal monitoring strip 6.

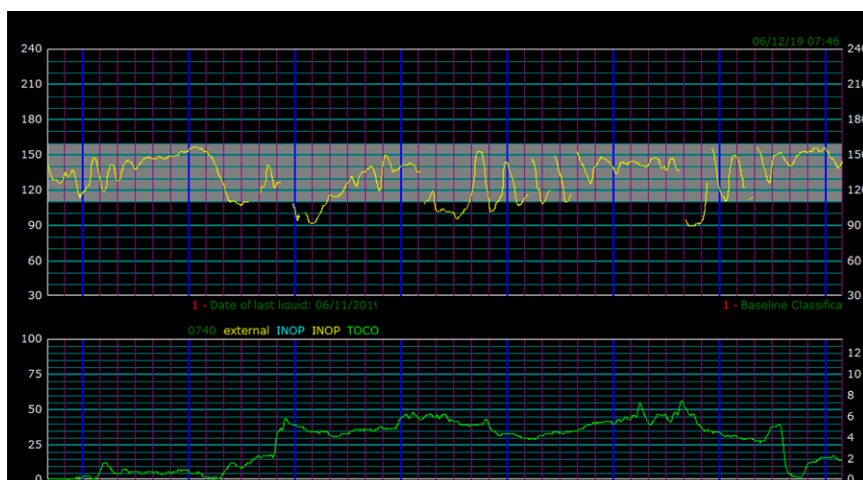


Figure 6. Electronic fetal monitoring strip 6.

Findings in EFM strip 6 are as follows (Fig 6).

- Baseline rate: Difficult to establish a clear baseline; requires 2 minutes (does not have to be continuous), which is not present in this panel
- Baseline variability: Absent
- Episodic patterns: Recurrent decelerations
- Periodic patterns: None
- Uterine contractions: Not clearly present
- Interpretation: Category III tracing
- Differential diagnosis: Umbilical cord compression, nuchal cord, and uterine rupture, nonreassuring tracing
- Action: Expedient delivery

An unscheduled repeat cesarean was performed, and on entering the abdominal cavity, the fetal arm was extruding through the uterus into the abdominal cavity and uterine rupture was diagnosed. The infant was delivered and brisk uterine bleeding was controlled with suturing. Intermittent uterine atony was noted, which was treated with uterotonics and transfusion of 2 units of packed red blood cells. A viable male infant was delivered to the awaiting pediatric team and resuscitation was immediately initiated, including continuous positive airway pressure. The Apgar score was 1, 5, and 7 at 1, 5, and 10 minutes, respectively. The umbilical cord gases are shown in Table 2. The term neonate was admitted to the NICU for further management and was noted to be vigorous on arrival. The infant's birthweight was 3,075 g, an evaluation for infection was negative, and brain ultrasonography finding was normal. The infant spent 5 days in the NICU and was then discharged.

## DISCUSSION

Uterine rupture is a rare obstetric complication occurring in less than 1% of scarred pregnant uteruses, including in

women with a history of myomectomy. It can also occur in women with unscarred uteruses, but to a much lesser extent. Complete uterine rupture is full-thickness separation of the myometrium with expulsion of the fetus, fetal parts, or placenta to the abdominal cavity. The US National Birth registry data for 2013 provides information on 90% of births from 41 states and the District of Columbia. The data show that the rate of uterine rupture is more than 7 times higher for women with a failed trial of labor having a repeat cesarean (495.4 per 100,000 live births) compared with repeat cesarean without labor (65.6/100,000 live births). (1) Although uterine rupture is a rare event, its occurrence is disastrous and has the serious perinatal consequence of intrapartum death of usually a term infant. The Medical Birth Registry of Norway reports a 26.2% infant death rate from uterine rupture in their data of over 2 million births from the years 1967 to 2008. Analysis of their data from 2000 to 2008 demonstrated a decrease in infant mortality from uterine rupture but the rate was still 15%. (2) Other morbidities associated with uterine rupture include neonatal asphyxia, hypoxic-ischemic encephalopathy, and severe maternal morbidity as a result of hemorrhage.

The most common pathologic FHR tracing associated with intrapartum uterine rupture is fetal bradycardia that is terminal in most cases. However, fetal bradycardia was not

TABLE 2. Arterial Umbilical Cord Gas Values for the Infant

pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS	BICARBONATE (mmol/L)
6.99	77	38	-12.50	17

present in our case; rather the predominant FHR tracing abnormality was recurrent variable decelerations, loss of baseline variability, and progression of decelerations with an episodic pattern (no obvious contractions). A population-based, case-control study sought to determine whether there are any cardiotocographic findings that could predict uterine rupture. (3) The Danish birth registry of over 62,000 women identified 181 complete uterine ruptures (0.5%) in this population. Fetal tracings were available for 53 uterine rupture cases and 43 matched controls of women who intended to have a VBAC. Nineteen obstetric subspecialists from leading obstetric departments in Denmark and Sweden, also described as having over a decade of clinical experience, were blinded to the clinical information from their cases and controls. They analyzed FHR tracings obtained within the last 4 hours before delivery. The study found that during the first stage of labor, before complete cervical dilation, suspicious FHR tracings were equally present in approximately half of both uterine rupture cases and controls; moreover, pathologic tracings were present in 77% of cases and 53% of controls. (3) Terminal bradycardia tracings require immediate intervention and leave little doubt that urgent delivery should be performed; therefore, these FHR tracings were removed by the investigators before review by the blinded obstetric subspecialist to prevent bias. Terminal bradycardia tracings were found only among the uterine rupture cases and not the controls. (3) The study found that in high-risk laboring women who have a scarred uterus, there are no specific FHR tracings that can actually predict uterine rupture. This is because pathologic FHR tracings are equally present in women undergoing a trial of labor who do not have uterine rupture. (3) Current expert opinion takes into account the unpredictable nature of uterine rupture and advises that laboring high-risk women with a scarred uterus should be in facilities that are equipped to perform urgent cesarean deliveries, and have an obstetrician, anesthesiologist, and pediatrician who are immediately available. (4) This recommendation is the most

significant and likely to have the greatest impact on infant outcome because delivery in less than 20 minutes was associated with improved infant outcomes and decreased infant death in cases of uterine rupture. (2)

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the significance, interpretation, and management of abnormalities or changes in fetal heart rate patterns during labor including reassuring and nonreassuring and indeterminate patterns.
- Know the diagnosis and management of maternal/fetal blood loss such as placenta previa, placenta abruption, vasa previa, and maternal-fetal hemorrhage.
- Know the incidence, causes and pathophysiology, including cellular abnormalities, of acute perinatal asphyxia.
- Know the interpretation of umbilical cord blood gas and pH values.

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## Strip of the Month: Laboring the High-Risk Gestation

Kafui A. Demasio and Katherine Ryken

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DOI: 10.1542/neo.20-11-e670

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## Multiple Missteps and System Failures Cause Kernicterus in 2 Infants

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### CASE 1

A 3,350-g, 38-week-gestation Asian female infant is delivered via vacuum-assisted delivery. Her Apgar scores were 3 and 8 at 1 and 5 minutes, respectively. Her physical examination findings were normal. A 4% weight loss was found at 25 hours, which was 12 hours before discharge. She was not weighed again. She was exclusively breastfed and discharged at 37 hours. *The plaintiff neonatologist pointed out that tracking an infant's weight provides a useful assessment of adequacy of breast milk intake and that a loss greater than 3% at 24 hours should have prompted an evaluation; the plaintiff discussed that at a minimum, the infant should have had a repeat weight check for accuracy and another weight assessment before discharge, and if equivocal, a weight check the following day. A weight measurement immediately before and after breastfeeding is very useful.* The bilirubin level was not evaluated before discharge. *The plaintiff neonatologist was critical of this omission, especially because this infant had multiple risk factors including Asian ancestry, vacuum-assisted delivery, perhaps excessive weight loss, early discharge, and exclusive breastfeeding.* The mother was instructed to call for a pediatric appointment in 5 days, but when the mother tried to make an appointment, she was told that no appointments were available until the infant was 7 days old. *The plaintiff neonatologist was critical of the infant not being assessed sooner because of the various risk factors.* When the infant was evaluated by the pediatrician at 7 days, the mother shared with the physician that the infant's eyes were very yellow. *According to the mother's deposition, her findings prompted the pediatrician to order a bilirubin level.* The pediatrician's note reflected that the infant's findings were normal except for icteric sclerae. *The plaintiff neonatologist was critical that the bilirubin was not ordered immediately.* The pediatrician told the nurse in his office that if the infant's bilirubin value was greater than 18 mg/dL (308  $\mu\text{mol/L}$ ) then home phototherapy should be considered and told the mother to expose the infant to indirect sunlight. *The plaintiff neonatologist was critical of these approaches.* Two hours after being seen by the pediatrician, the infant had a bilirubin level sent. Four hours after the blood was collected, the results of the bilirubin level were faxed to the pediatrician's office. The value was greater than or equal to 30 mg/dL (513  $\mu\text{mol/L}$ ). When the pediatrician was apprised of this result, he asked his nurse to contact the mother and to tell her to bring the infant to the emergency department (ED). *The plaintiff neonatologist was critical of the casualness of this approach, stating that the pediatrician should have called the mother and coordinated the findings with a neonatologist because the bilirubin level was dangerously high; by sending the infant to the ED, an unnecessary delay in interventions occurred.*

The infant arrived at the ED 8 hours after the visit to the pediatrician. The ED triage was performed as "nonurgent." After the ED physician took this history from the mother, he conducted a physical examination, urinalysis, ordered a chest

**AUTHOR DISCLOSURE** Dr Sims has disclosed that she has been compensated for reviewing records and providing testimony in some of the cases highlighted in Legal Briefs. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



radiograph, a complete blood cell (CBC) count, and a bilirubin level. The mother reported that the infant had not passed a stool for 4 days and her diapers were not wet frequently. The infant's weight was down 10%. These laboratory tests were performed 11½ hours after the pediatrician visit. The CBC, chest radiograph, and urinalysis findings were normal. The bilirubin value was 26.7 mg/dL (457 µmol/L). The physician in the ED asked for phototherapy lights to be brought to the ED, but was told none were available. Three hours after the bilirubin result, the ED physician contacted a local university for transport, but because no beds were available, another medical center was contacted. The infant arrived at this facility where triple phototherapy was initiated; this was approximately 24 hours after the mother had arrived at the pediatrician's office the day before. A third-year pediatric resident evaluated the infant and noticed jaundice over the entire body, good tone, and a positive suck. The resident ordered a stat bilirubin level and contacted her attending general pediatrician 1 hour later. The bilirubin level was measured 90 minutes after admission, with the result available 30 minutes after being drawn. The total bilirubin was 30 mg/dL (513 µmol/L) and the direct bilirubin was 0.8 mg/dL (13.7 µmol/L). The neonatologist was contacted and ordered another bilirubin level. **A repeat bilirubin was 29.8 mg/dL (509 µmol/L). The plaintiff neonatologist was critical of unnecessary delays and that an immediate exchange transfusion was not given upon admission.** The infant continued to receive triple phototherapy. An evaluation for the cause of the indirect hyperbilirubinemia included a direct antiglobulin test (DAT), blood group and type, glucose-6-phosphate dehydrogenase level, CBC, and a urinalysis. Results of all these tests were unremarkable. The bilirubin level gradually came down and she was discharged at 10 days. At 9 months of age, the infant was noted to have developmental motor delay. Computed tomography was performed and was negative. **Plaintiff experts pointed out that unremarkable neuroimaging result does not negate the diagnosis of kernicterus.** At 3 years of age, the child had dystonic-ataxic cerebral palsy, but normal cognitive and language development. The pediatricians, the ED physician, and neonatologist were sued. **Plaintiff experts contended that the pediatrician who discharged the infant should have evaluated the bilirubin level at discharge as well as the next day and followed the bilirubin levels closely because the infant had many risk factors for developing severe hyperbilirubinemia. At the office visit, the pediatrician should have ordered a stat bilirubin and after the results returned, should have appreciated the danger of its high level and coordinated the infant's care directly with a neonatologist. The pediatrician and neonatologist needed to respond in a more timely manner to the incoming infant with**

**such a dangerously high level of bilirubin. The defense argued that all of the actions of the physicians met the standard of care and this was a rare and unpredictable situation. The treating and defense neonatologists said that because the infant's physical examination findings were normal, it was acceptable to follow the infant's bilirubin levels without an exchange transfusion because the procedure has risks. The plaintiff responded that a normal physical examination is not a valid standard to refrain from giving an exchange transfusion when the bilirubin level is very high.** The case settled without going to trial.

## CASE 2

A 3,312-g, 40-week-gestation female infant was born to a gravida 3, para 2, 39-year-old Hispanic woman who had an unremarkable pregnancy and a normal spontaneous vaginal delivery. **The mother stated in her deposition that her previous 2 children had normal neonatal courses except that they had jaundice but did not receive phototherapy. They are both healthy and doing well during early childhood.** According to the hospital records on the current birth, the laboratory reported a positive DAT result that was detected prenatally and was recorded on the infant's records by 3 hours after birth. The prenatal records from a perinatologist showed anti-Kell antibodies on the prenatal screen. The records do not reflect that the delivering obstetrician was informed, but it does show that the mother was informed several months before delivery. The infant's records reflect a positive DAT, but do not reflect anti-Kell antibodies. Two bilirubin assessments were performed before discharge. The first was a transcutaneous evaluation at 6 hours of age that showed a bilirubin level of 6.5 mg/dL (111 µmol/L). The second was a serum assessment at 22 hours of age that showed a total bilirubin of 9.1 mg/dL (156 µmol/L) with a direct bilirubin of 0.7 mg/dL (12 µmol/L). **The plaintiff neonatologist pointed out that because the medical records showed that the DAT was positive, the cause should have been investigated by the hospital and the pediatrician. This information was not acknowledged by the nurses or the pediatrician in the records. The laboratory personnel did not communicate any details about this finding by phone. The plaintiff neonatologist was critical that an evaluation was not conducted to determine the cause of high bilirubin, pointing out that both readings were high with respect to the newborn's time after birth. Because the bilirubin level at 6 hours was 6.5 mg/dL (111 µmol/L), the serum bilirubin should have been evaluated immediately, phototherapy started, and the cause for hyperbilirubinemia explored. The treating pediatrician, nurses, and laboratory blamed each other for not appreciating or**

**communicating the positive DAT result.** The infant did not receive phototherapy, was being exclusively breastfed, and had a weight loss of 4% at the time of discharge at 34 hours of age. The first follow-up appointment was at 9 days of age at which time the pediatrician noted the physical examination to be normal except for jaundice. **The plaintiff neonatologist was critical of the long interval between discharge and the first follow-up appointment, especially because the infant was discharged with a very high level of bilirubin.** A stat total bilirubin was sent at this point and was found to be 30 mg/dL (513  $\mu$ mol/L) with a direct bilirubin of 0.7 mg/dL (12  $\mu$ mol/L). The mother was told to supplement breastfeeding with formula and to bring her infant to the ED for further evaluation. **The plaintiff neonatologist was critical of this approach, stating that a neonatologist should have immediately been contacted and arrangements made for transfer to a facility where it was possible to give an exchange transfusion, instead of wasting time in an ED.**

Several hours after the pediatrician's visit, the mother arrived at the ED where the physician noted that the infant had jaundice, increased tone, intermittent back arching, and a high-pitched cry. The infant's weight was down 10% from her birthweight. A repeat total bilirubin level was 31 mg/dL (530  $\mu$ mol/L). The infant was immediately transported to a NICU across town where she was placed under intense phototherapy. The interval from the pediatrician's office to arriving at the referral center was 8 hours. A laboratory evaluation showed the bilirubin to be 31 mg/dL (531  $\mu$ mol/L) and the DAT result to be positive. The mother's blood type was O, Rh positive and the infant's blood type was A Rh positive and anti-Kell antibodies were present. Intravenous immunoglobulin (IVIG) was given, followed by a double volume exchange transfusion pushed through the internal jugular vein and pulled from an umbilical venous catheter. At the start of the exchange transfusion, it had been over 10 hours after the pediatrician's visit. The infant was also given IVIG after the exchange transfusion. The postexchange bilirubin was 19.3 mg/dL (330  $\mu$ mol/L) and the level trended downward over the next several hours. Five days after the exchange transfusion, magnetic resonance (MR) imaging showed diffusely increased T1 signals in the globus pallidus, substantia nigra, and subthalamic nuclei; the MR spectroscopy result was normal. **The plaintiff neuroradiologist stated that this was consistent with kernicterus.** On the day of discharge, 7 days after the exchange transfusion, the infant had normal physical findings, but on follow-up examination, she developed athetoid cerebral palsy and developmental delays. The hospital and the pediatrician were sued. The case settled without going to trial.

## DISCUSSION

Most newborns develop jaundice and it is mostly benign. However, because of the potential toxicity of bilirubin, it is critical to identify infants who are likely to develop severe indirect hyperbilirubinemia as demonstrated in the 2 cases described here. Many risks in the healthy newborn can be identified at birth or soon thereafter: for example, based on the history (infants of diabetic mother, Asian ethnicity), physical examination findings (bruising, cephalohematomas, gestational age <38 weeks), and laboratory tests (maternal-infant blood incompatibilities, positive DAT result, high hematocrit counts). Serial bilirubin measurements and timely intervention are necessary to avoid the development of acute or chronic bilirubin encephalopathy. Universal predischarge screening is recommended and can be accomplished transcutaneously or by measuring the total serum bilirubin level. Bilirubin levels should be evaluated in the context of hour-specific nomograms. Plotting the result on a nomogram helps to determine the risk of subsequent significant hyperbilirubinemia. By evaluating the bilirubin level with respect to the hour after birth, the clinician can determine the infant's predischarge risk by plotting a single value at a point in time or with serial values. An assessment of the rate of rise of bilirubin levels helps to identify infants who may develop significant hyperbilirubinemia. The rate of rise is useful as a red flag (>0.2 mg/dL [3.4  $\mu$ mol/L] per hour), underscoring a need for further evaluation or for instituting phototherapy. The clinician should be proactive in predicting subsequent bilirubin levels based on the risk factors noted on history, physical examination, or laboratory testing; assessing the rate of rise; and the predischarge screening on hour-specific nomograms; management should be guided accordingly, that is, either provide immediate treatment or institute close follow-up in the hospital or after discharge.

Attention to weight changes from birthweight is critical to determine the adequacy of breastfeeding because inadequate feeding causes an exacerbation of physiologic hyperbilirubinemia through decreased caloric intake and dehydration, with an increase in the enterohepatic circulation. Data to understand the normal weight loss in formula and breastfed infants are available. Data on weight loss are available for vaginal and cesarean deliveries. Ethnicity influences the need for a higher degree of surveillance in a select group of infants as it did in case 1. Asian newborns who are predominantly breastfed have higher peak values (10–14 mg/dL [171–239  $\mu$ mol/L]) compared with white and black newborns, necessitating closer monitoring. Extravascular blood from difficult deliveries also places a neonate at higher risk of hyperbilirubinemia because the degradation of the

extravascular blood from bruising contributes to the bilirubin pool as seen in case 1. Once a dangerously high level is reached, it is imperative that timely communication, transport, and institution of intervention occur. Excessive weight loss, lack of bilirubin screening, Asian ethnicity, and vacuum extraction, along with lack of timely follow-up after discharge and inertia when a dangerously high level was detected, contributed to the bilirubin encephalopathy in case 1.

An infant born with hemolytic disease, as in case 2, requires high vigilance to avoid the adverse consequences of hyperbilirubinemia. Timely laboratory evaluation and documentation and the clinician's appreciation of the status of a positive DAT result are crucial very soon after birth. A positive DAT status must be known before discharge because hemolysis is a crucial risk factor for significant hyperbilirubinemia. Although hyperbilirubinemia from ABO incompatibility may be severe and unpredictable, it is generally mild to moderate in severity. Hemolytic disease of the newborn secondary to Rh disease has decreased in severity because of RhoGam administration during pregnancy, therefore, anti-Kell has become relatively more important as it can cause very severe hemolysis. About 9% of the population is Kell positive. Hemolytic disease of the newborn secondary to anti-Kell is caused by a situation in which the pregnant woman has an absence of a Kell antigen on her red blood cells (RBCs) but is exposed to RBCs with the presence of a Kell antigen. This situation can result from the mother having received a prior transfusion with Kell-positive blood or from current or former pregnancies with a fetus who was Kell-positive. The maternal response to transfused or leaked RBCs results in the creation of anti-Kell antibodies that cross the placenta and attach to the fetal RBCs and cause hemolysis. A drop of 1 g of hemoglobin results in the production of 35 mg of bilirubin. Thus, even a small amount of hemolysis creates a huge challenge for the newborn who cannot rely on the maternal liver to metabolize the excess bilirubin. Because adverse neurologic sequelae are distinctly greater for hyperbilirubinemia secondary to hemolytic disease compared with nonhemolytic causes, knowledge of the DAT result before discharge of the

newborn is critical. The multiple missteps in the 2 current cases led to the development of kernicterus in both infants. Kernicterus is preventable and should be a "never" disease if a systems-approach and institutionalized practices based on seamless care become standard and routine.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathologic findings of kernicterus.
- Know the factors that increase the risk of the development of kernicterus.
- Know the clinical features of kernicterus.

## Suggested Readings

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**Update on Erythropoiesis-Stimulating Agents Administered to Neonates for Neuroprotection:** 1. B; 2. D; 3. C; 4. C; 5. A.  
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Maureen E. Sims

*NeoReviews* 2019;20:e683

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## A Neonate With a Perineal Lesion

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### THE CASE

A full-term female newborn is noted to have a perineal lesion a few hours after birth.

#### Prenatal and Birth Histories

- Born to an 18-year-old gravida 1 woman
- Prenatal maternal laboratory findings: Normal, except varicella nonimmune
- Full integrated screen with elevated inhibin level (2.02 multiple of the median)
- Normal nuchal translucency (2.1 mm)
- Maternal medications: Prenatal vitamins
- Estimated gestational age: 39 4/7 weeks
- Spontaneous vaginal delivery with meconium-stained amniotic fluid; no trauma with delivery
- Infant cried immediately after birth and did not need any resuscitation; cord clamping occurred at 2 minutes
- Apgar score: 8 at 1 minute and 9 at 5 minutes
- Birthweight was 4.16 kg and infant was large for gestational age

#### Presentation (Day 0)

On initial physical examination of the infant at 3 hours after birth, a wet erythematous sulcus was noted in the perineum extending from the posterior fourchette to the anterior edge of the anus (Fig 1). Bilateral preauricular ear tags were noted and the remainder of the physical examination was normal. Pediatric surgery was consulted because of a concern for a perineal tear.

### PROGRESSION

#### Vital Signs

- Heart rate: 158 beats/min
- Respiratory rate: 48 breaths/min
- Temperature: 97.2°F (36.2°C)

#### Physical Examination (Day 0)

- Birthweight = 4.16 kg (97th percentile); birth length = 52 cm (94th percentile); head circumference = 35 cm (83rd percentile)
- Head: Normocephalic; normal, open, flat fontanelles; positive caput succedaneum, symmetric facies; patent nares; intact palate; red reflex deferred; positive bilateral small preauricular ear tags
- Oral cavity: Pink mucosae, intact palate, normal sucking, and rooting reflex

**AUTHOR DISCLOSURE** Drs Eskandar-Afshari, Danzer, Lee, and Ragavan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





Figure 1. Neonate with perineal lesion.

- Lungs: Clear, equal breath sounds; no respiratory distress
- Cardiovascular: Normal S<sub>1</sub>, S<sub>2</sub>; regular rate and rhythm; no murmurs or gallops
- Abdomen: Soft; nondistended; bowel sounds present in all quadrants; 3 vessel cord
- Genitourinary: Normal external female genitalia except for wet sulcus noted, extending from the posterior fourchette to the anterior edge of the anus, anus patent
- Skeletal: Spine appears normal
- Skin: No icterus, birthmarks, or other rashes
- Neurologic: Alert and active; normal tone; age appropriate; symmetric Moro

## DIFFERENTIAL DIAGNOSIS

- Anal fissure
- Contact dermatitis
- Congenital perineal groove
- Infection
- Lichen sclerosis
- Perianal pyramidal protrusion
- Perineal trauma
- Sexual abuse
- Ulcerated hemangioma

## ACTUAL DIAGNOSIS

The newborn nursery course was unremarkable. The infant breastfed well and received supplemental formula per maternal request. She had a normal voiding pattern. She passed stools in a normal fashion through the anus. She was clinically diagnosed to have a congenital perineal groove (Fig 2). Bacitracin ointment was applied 4 times daily to the perineal groove per pediatric surgery recommendations. The infant passed the bilateral hearing screen and was discharged from the hospital at 2 days of age with instructions to follow up with the pediatrician in 1 to 2 days.

## WHAT THE EXPERTS SAY

A congenital perineal groove is an uncommon malformation characterized by a wet erythematous sulcus extending from the posterior part of the fourchette to the anterior opening of the anus. (1)(2)(3)

Stephens (4) described the perineal groove of 4 infants in 1968 to have 3 common features: normal formation of the urethra and the anterior two-thirds of the vagina, hypertrophy of the minor tails that border the perineum and extend posteriorly to join or surround the anus, and a wet sulcus extending from the posterior fourchette to the anus. (3)(4)

The pathogenesis of a perineal groove is unclear. Hypotheses about the embryologic origin of this malformation include incomplete fusion of the perineal raphe or medial genital folds, a uroanal septum defect, or a relic of an open cloacal duct. (1)(3)(5)(6) The condition is more commonly found in female patients, with a few reported cases in male patients. (3)(7)(8)

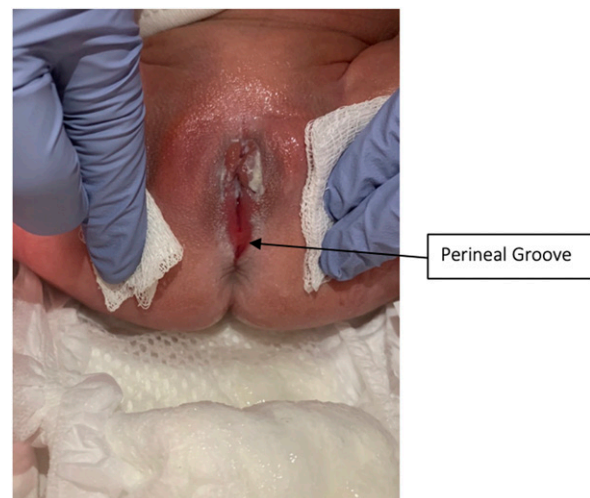


Figure 2. Neonate with congenital perineal groove depicted by arrow.

Diagnosis is made by clinical examination. (9) The malformation is usually asymptomatic, generally epithelializes by 1 year of age, but sometimes takes longer, up to 2 years of age. It does not require treatment or further intervention unless there are complications or cosmetic correction is required. (3)(9) Cases are usually isolated and without other coexisting urogenital anomalies; therefore, routine imaging is not usually recommended, but can be considered. (8)(9)

Since this condition is generally unknown to many medical providers, it is pertinent to recognize a perineal groove and differentiate it from other diagnoses such as anal fissures, diaper dermatitis, infection, lichen sclerosis, ulcerated hemangioma, perianal pyramidal protrusion, and especially perineal trauma and sexual abuse, to avoid inaccurate diagnoses and subsequent unnecessary interventions. (8)(9)

Surgical treatment for congenital perineal groove is considered only after 2 years of age if there is concern for recurrent infection and persistent mucus drainage or for a cosmetic reason. (1)(9) The procedure entails excision of the perineal groove, suturing of the site, and then application of a chemical glue to cover the sutures and protect the area from becoming infected. (1) Complications of the condition itself are rare and may include urinary tract and skin infections. (1)(9)

Perineal trauma and sexual abuse were not suspected, because the delivery was uncomplicated and the finding was noted immediately after birth. A perianal pyramidal protrusion appears as a skin tag or fold in a similar location to the congenital perineal groove; however, our patient did not have this finding. (10) Lichen sclerosis is a chronic inflammatory condition of the skin and mucosa that most commonly affects the anogenital region of prepubertal or postmenopausal females. The lesions in lichen sclerosis typically initially appear as white, flat-topped papules, thin plaques, or atrophic patches. The lesions in lichen sclerosis can become hyperpigmented and purpuric, and erode and ulcerate, which did not fit with our patient's physical examination finding or her age. (11) Anal fissures usually occur because of the passing of large, hard stools due to constipation and present with pain and bleeding with bowel movements. There was no evidence of diaper dermatitis or infection on physical examination, and these conditions do not normally appear immediately after birth. Infantile hemangiomas usually present in early infancy as a "localized blanching or localized macular telangiectatic erythema" followed by endothelial cell proliferation which, when rapid, can lead to ulceration. (12) This was not consistent with the physical examination findings or the timing of the lesion in our patient. Based on the history and

clinical exam finding, our patient was diagnosed with a congenital perineal groove. It is imperative for physicians who take care of newborns to recognize this finding and diagnose it accurately since it can be easily misdiagnosed and therefore mismanaged. Given its rarity, it should be shared in the literature and medical community so we can shed light on this uncommon diagnosis.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Environmental factors.

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# Psychosocial Stress and Adversity: Effects from the Perinatal Period to Adulthood

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## Education Gaps

It is essential to acknowledge the significant effects of psychosocial factors and resultant stress on outcomes and development of children. Understanding how the effects of psychological stress can act additively or synergistically with other biological and genetic influences can potentially lead to the development of new approaches to improve patient care and outcomes.

## Abstract

Early exposure to stress and adversity can have both immediate and lasting effects on physical and psychological health. Critical periods have been identified in infancy, during which the presence or absence of experiences can alter developmental trajectories. There are multiple explanations for how exposure to psychosocial stress, before conception or early in life, has an impact on later increased risk for developmental delays, mental health, and chronic metabolic diseases. Through both epidemiologic and animal models, the mechanisms by which experiences are transmitted across generations are being identified. Because psychosocial stress has multiple components that can act as stress mediators, a comprehensive understanding of the complex interactions between multiple adverse or beneficial experiences and their ultimate effects on health is essential to best identify interventions that will improve health and outcomes. This review outlines what is known about the biology, transfer, and effects of psychosocial stress and early life adversity from the perinatal period to adulthood. This information can be used to identify potential areas in which clinicians in neonatal medicine could intervene to improve outcomes.

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### ABBREVIATIONS

ACE	Adverse Childhood Experiences
EEG	electroencephalography
HPA	hypothalamus-pituitary-adrenal

## Objectives After completing this article, readers should be able to:

1. Define stress taxonomy and describe the terms used to define stress and stress transfer in humans.



2. Explain the biological and social basis for stress transfer between generations.
3. Identify disruptive effects of toxic stress and early childhood adversity on development and describe methods to support parents before, during, and after pregnancy.

## BACKGROUND

Environmental and genetic influences on human neurodevelopment begin prenatally and continue through adolescence and early adulthood. (1) Although studies have shown that the architecture of the brain is established during the early periods of development in utero, accumulating evidence has demonstrated that events before conception, such as adverse psychosocial exposures (eg, history of maltreatment when the pregnant woman was a child), (2) may influence the development of later generations. Traditional understanding of human development has focused on the biological and genetic influences on development, health, and disease without considering psychosocial variables. More recently, characterization of specific adverse exposures has provided evidence supporting the critical role that psychosocial factors have in modifying these developmental processes. However, the pathways by which adverse psychosocial exposures influence outcomes are not well understood. Thus, the relative risk associated with such exposures, and discovery of modifying factors that connect these exposures and neurodevelopmental outcomes, remain unclear. (3) This review aims to summarize what is known about the biological basis, intergenerational transmission, and effects of psychosocial stress and early life adversity from the perinatal and newborn period to adulthood. The Table provides definitions of terms used in this review that are associated with stress and the transfer of stress in humans.

## HOW IS STRESS TRANSFERRED TO THE FETUS?

From a biological perspective, stress can be defined as an experience that leads to the activation of well-defined neurobiological systems that preserve viability through allostasis. (4) Stress response is a part of our daily life as a mechanism of survival. However, in chronic and persistent degrees it is known to cause harm. But many details regarding which stressors undergo intergenerational transfer, and how such transfer occurs, remain unclear.

Animal models have provided evidence that stress in pregnancy can lead to a range of long-term effects on the

offspring such as reduced attention, problems in behavior, and increased risk in general susceptibility to mental health issues. (5) Potential mechanisms for the transfer of maternal stress responses to the fetus and potential intergenerational stressors include transplacental transfer of bioactive molecules, autonomous fetal responses to changes in the uterine environment, and epigenetic mechanisms. (6) In the case of bioactive molecules, fetal exposure to increased maternal cortisol transfer across the placenta could lead to impaired development of the hypothalamus-pituitary-adrenal (HPA) axis. Alterations in the reactivity of the HPA axis may then be a mechanism for the increased insulin resistance observed in populations exposed to adverse stressors. (5)(7)(8) Other maternal stress-response molecules that have been described to cross the placenta in animal models include catecholamines, reactive oxygen species, cytokines, serotonin, and tryptophan.

In addition, alterations to the maternal microbiota could affect the in utero environment indirectly or be transferred to the neonate during delivery. These bioactive molecules and microbiota could also act synergistically to alter neurodevelopment. Recent reviews have discussed the vulnerabilities to maternal adverse stressors during the embryonic and fetal periods. (2)(6)(9)

Adverse in utero experiences may also directly affect the fetus. Potential autonomous effects of stress could be explained by biological aging with modification of telomere length, a marker of cellular aging that is associated with physical health risk. (10) Environmental factors such as maternal stress and socioeconomic status in utero are associated with accelerated telomere shortening at birth. (11) Although no specific mechanism has been identified, indirect evidence suggests that maternal HPA axis functioning during pregnancy could be involved. (12)(13)

Studies to assess the transfer of stress and the impact of adverse experiences across multiple generations have used mice and other animals with rapid generation capabilities. These studies have observed behavioral changes not only in the first offspring but also in subsequent generations. (14)(15) In a study to test the intergenerational effect of early stress, mice exposed to chronic and unpredictable maternal

**TABLE. Definitions Associated with Stress and Transfer of Stress in Humans**

TERM	DEFINITION
<i>Allostasis</i>	Process (physiological or behavioral change) of adaptation by which the body responds to stressors to regain homeostasis or balance. (16)(17)(18)(19)
<i>Allostatic load</i>	Changes in the brain and body that can lead to disease from the burden of chronic stress. Referenced as "the wear and tear on the body," which accumulates as the body is exposed to chronic and cumulative stress. (17)(18)(19)
<i>Biological embedding of adversity</i>	A mechanistic process by which experience gets "under the skin" and alters health and development. Developed by Hertzman in 2012 to help explain social gradients in health. (20)
<i>Critical period in development</i>	Windows of heightened plasticity during brain development. During this time, adequate environmental input is required for adequate development of particular brain circuits. (21)(22)(23) If there is no stimulus or a noxious one, the development could be compromised and lead to developmental delay.
<i>Early life adversity</i>	Negative childhood experience associated with an increased lifetime risk of poorer health and social outcomes. (24) This term has now been used widely to talk about psychosocial adversity. (25)
<i>Eco-bio-developmental framework</i>	Proposed by the American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health in 2012 as a multidimensional framework (including personal experiences, environment, genetic predispositions) to understand and approach health and disease. It is a good illustration of how early experiences and environment can modify genetic predispositions, thus changing brain architecture and as a consequence, long-term health. (26)
<i>Epigenetics</i>	An epigenetic change happens with the combination of mechanisms that confer long-term programming to gene activity and could change gene function without changing its gene sequence. (27)(28) Epigenetic mechanisms regulate transcriptional processes where gene expression activates and deactivate genes and determines which proteins are transcribed. Epigenetic changes have been associated with different hypotheses involving social behavior (eg, stress) in animal models. (28)(29)
<i>Psychosocial adversity</i>	Adverse experiences are psychosocial hazards that can affect development, particularly if present during critical periods of development. Negative experiences relating to a child's psychosocial environment (eg, maltreatment, caregiver psychopathology, violence exposure, depriving care environments) and relationships that increase the risk of poorer health and social outcomes over the life course. (30)
<i>Stress</i>	Defined as "a physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation." (31) Physiologic responses to stress through the activation of neurobiological systems (hypothalamus-pituitary-adrenal axis and the sympathetic adrenomedullary system) have been well-defined for years. (19)(32)(33)(34) Transient increases in stress hormones are protective and essential for survival, but excessively high levels or prolonged exposures could be harmful. (35)
<i>Toxic stress</i>	The National Scientific Council on the Developing Child described 3 concepts for the different types of stress responses in children, including "positive, tolerable, and toxic" stress depending on the intensity and duration of response, and as a result, the potential to cause long-lasting consequences. (36)(37) Toxic stress is defined as the excessive or prolonged activation of the physiologic stress response systems in the absence of the buffering support by a stable and responsive relationship that reinforces healthy adaptations to stress. (38)
<i>Transgenerational transmission*</i>	Transmission of environmental adversity from F0 to F3 or F4—exposure of the past generation to the environment or stressor during pregnancy that will still be present in the third generation (the first generation that is not directly exposed), possibly because of epigenetic mechanisms. (29)(39)
<i>Intergenerational transmission*</i>	Transmission of environmental adversity from F0 to F1—direct exposure of the parental (F0) and subsequent generation (F1) to the stressor by the developing germ cell or fetus. (29)(39)

\*Transmission of environmental adversity effects has been established in animal models.

separation in the first 2 weeks of postnatal age demonstrated depressionlike behaviors as adult mice. (40) Similar results have been seen in primate studies where exposure to early

maltreatment and separation was associated with altered social behaviors, including increased fearfulness and anxiety, as well as social and sexual dysfunction as adults. (41)

One study characterized an example of transgenerational effect (42) when stress and anxiety in adult mice were induced by unforeseeable maternal separation and maternal stress early in life (14 days after birth). Antisocial, depressive, and risk-taking behaviors, as well as impaired memory and altered serotonergic 1A receptor in the brain, were found not only in the affected mice as adults but persisted across 2 generations that had not been exposed to stress. (42) Such multigenerational inheritance patterns could be because of learned behaviors, but it is likely that adverse experiences may mediate epigenetic modifications of DNA that lead to changes in programming physiology and behavior, ultimately modifying the risk factor for diseases in adulthood. (43)(44) Thus, a deeper understanding of the mechanisms could identify potential targets for therapeutic interventions.

Although most studies describe descendant interactions coming from mothers, a few studies describe a potential influence of paternal stressor exposures via epigenetic variation in the patriline. (45) In addition, fathers may indirectly influence the descendants by being supportive or not supportive of their partners. (5)(6)(46)(47) To best care for the whole family, ongoing work to better understand the contribution of each family member to health and outcomes is important.

## CONSEQUENCES OF PRENATAL EXPOSURE TO STRESS AND ADVERSITY

It is known that the intrauterine environment significantly influences growth and development in the prenatal period. A detailed review of brain development has been previously described. (48) In brief, brain development starts early in the embryonic period that begins at conception through the eighth week of gestation. During this period, rudimentary structures of the brain and central nervous system are defined. By the third week of gestation, through a process called *neurulation*, the neural progenitor cells differentiate and form the neural plate. The neural plate eventually becomes the neural tube, the first brain structure that will later differentiate into the spinal cord and the brain. While these structures are forming, neuron production, migration, and differentiation take place. This long process continues through embryonic, fetal, and postnatal periods, extending to late adolescence as neuronal connections continue to develop. (48)

Accumulating evidence has identified that adverse environmental maternal factors during the fetal period, such as poor maternal nutrition, maternal obesity, and adverse stressors, are associated with effects that last well beyond the fetal period. Both human and nonhuman animal studies

have shown that fetal exposure to maternal stress can influence later stress responsiveness. (15)(49)(50) For example, mice exposed to adverse prenatal stress, such as spatial restriction and bright lights, were observed to have disrupted sleep patterns, altered activity of the HPA axis, increased anxiety-related behaviors, and difficulty with memory. (15) Human fetuses and infants exposed to maternal anxiety or depression demonstrate increased methylation of the glucocorticoid receptor gene in cord blood and increased cortisol responsiveness at 3 months of age, highlighting the ability of psychosocial exposures to affect gene expression. (49)

Vulnerable or critical periods have been identified during gestation, and adverse exposures during these periods can have negative effects on childhood behavior and emotional development, as well as increase the risk for metabolic, cardiac, and mental health problems later in life. (51)(52) These initial periods of development are characterized by increased brain plasticity, but also greater vulnerability. (9) For example, acute stress in a pregnant woman, such as experiencing a natural disaster, can alter the urine metabolic profiles of her children, (53) indicating alterations in multiple biological pathways. Poor clinical outcomes in neonates, such as the need for assisted ventilation or meconium aspiration syndrome, have also been observed after natural disasters. (54) In addition, elevated maternal stress has been associated with prematurity and lower birthweight in multiple studies. (55) A detailed summary of the evidence can be found in a recent critical review of the effects of prenatal stress on fetal and child development. (56)

More recently, new studies have demonstrated that infants exposed to maternal psychosocial stress have significant changes in brain electrical activity as detected with electroencephalography (EEG) as early as 2 months of age. (57) EEG holds great promise as a noninvasive test that can be performed serially during development. EEG was successfully used as an index of the association between caregiver stress and neurodevelopment in infants, making it a promising tool to identify indicators of risk and resilience in very young infants. (57)

## EXPOSURE TO STRESS AND ADVERSITY DURING INFANCY AND CHILDHOOD

During infancy and childhood, the brain continues to develop at a rapid pace. Critical or sensitive periods also exist after the fetal period, during which there is intense development of specific neural circuits such as those related to language development, hearing, vision, and socialization. At this time, both positive and negative experiences create

the foundation for future health and behaviors. (58)(59) These critical periods occur mostly in the first years of life when human brains have their greatest total number of synapses. (60) A longitudinal study in 2000 was able to demonstrate how these critical periods were affected in children with poor exposure to social and environmental stimulation when institutionalized at a very young age. (60)(61)(62)(63) It was previously thought that once these critical periods of development close, there was no way to regain plasticity. However, more recent work in a nonhuman animal model suggests that there might be an opportunity to reopen the periods and recover some lost function with appropriate stimuli. (21)(22) This indicates the potential for intervention after identification of at-risk individuals.

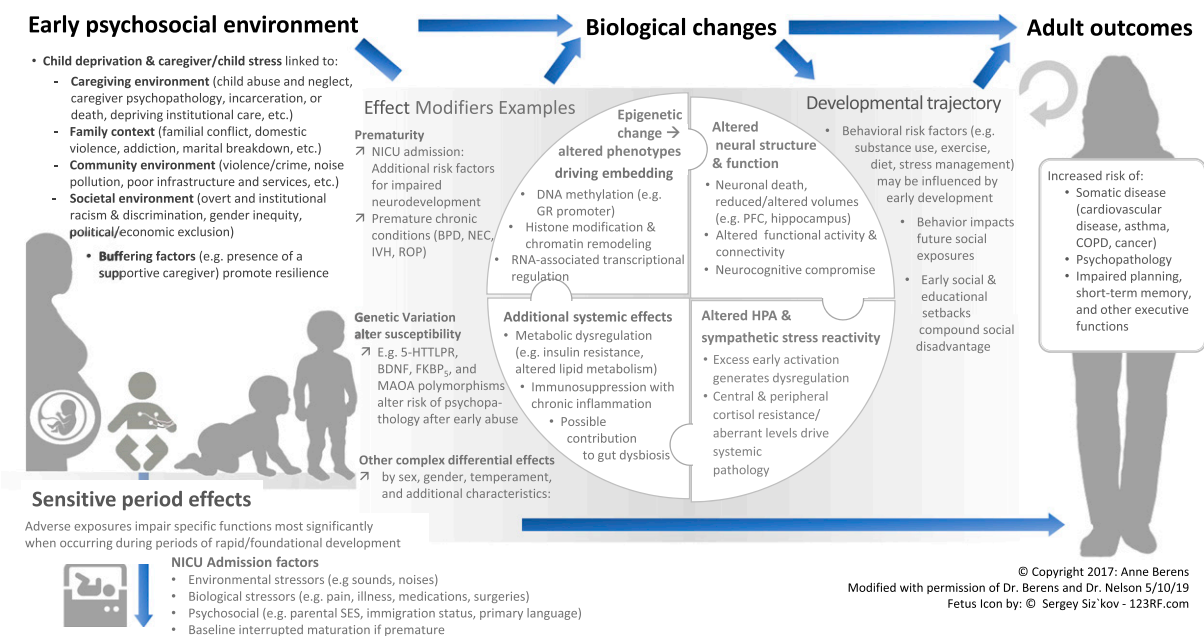
Early adversity during the postnatal period may modify neuroendocrine responses to stress secondary to changes in the developing neural circuits. This mechanism is thought to explain how adversity may affect the reactivity to stress in the future. (26)(64) Excessive or chronic stress activation with no buffer during childhood, referred to as *toxic stress*, (26)(36)(37) plays an important causal role in the intergenerational transmission of disparities in development, educational achievement, mental health, and health outcomes. (26) Figure 1 shows a conceptual model proposed by Berens et al about the different effects of early adversity across different axes (neural, endocrine, immune, and metabolic) and epigenetic processes during critical periods, which may explain the “biological embedding of childhood adversity.” (24)

Experiences with adversity can be exemplified in many different ways. Examples discussed in detail herein include poverty, immigration, and early illness.

## Poverty

In 2017, 17.5% (ie, 12.8 million) of the US population younger than 18 years lived in poverty, which is about 1 in 5 children, compared with 1 in 8 adults. (65) Child poverty has been used as an economic indicator of the well-being of children who, at a point in time, live in families whose resources are below a consistent threshold that is considered to be sufficient to meet basic needs (59) such as food security and stable housing. For example, 3 forms of housing instability (being behind on rent, experiencing multiple moves, and history of homelessness) have been associated with increased adjusted odds of adverse health outcomes compared with stable housing. (66)

Additional data suggest an increased risk of poor outcomes, particularly cognitive impairment and poor educational attainment, for children of low-income families. A cross-sectional study of children (ages 4–22 years) showed that children who live in low-income families had reduced gray matter volumes in the frontal and temporal cortex and the hippocampus, areas that have been associated with school readiness and achievement. A second study of children (ages 3–20 years) found similar effects of household income on brain development, particularly when income was below the poverty line; the study also demonstrated a



**Figure 1.** Biological embedding of early life adversity: A conceptual model. Printed and modified with permission from Anne Berens. Copyright Registration Number / Date: VAU001275841 / 2016-07-07

relationship among elevated cortisol levels, poverty, and measures of executive function. (32) Outcome disparities in children from low-income families have been associated with reduced parental cognitive input and increased environmental pollution. Being born into a poor family has been shown to strongly predict poverty status in the future. (33) All these data suggest that factors associated with poverty, not only income, are associated with increased risk for poor outcomes. Thus, poverty is more than just an indicator of material hardship but includes multiple layers of complexity that add or even interact synergistically.

## Immigration

As of 2017, about 44.5 million immigrants are living in the United States, and about 25% of those individuals are undocumented immigrants. (67) Between 2012 and 2016, 5.1 million children younger than 18 years lived in a household with an undocumented immigrant, which corresponds to 7% of the US population. (67)(68) Immigrant or foreign-born status has been identified as a risk factor for poor health for many reasons, such as migration itself being a period of significant adjustment and stress. (69) Immigrants are also more likely to have low socioeconomic status than nonimmigrant residents of the United States; in 2017, the poverty rate in the foreign-born population in the United States was 14.5% compared with 11.9% in the native-born population. (65) It is known that fear of deportation and anxiety in undocumented immigrants causes high levels of stress and anxiety to not only the undocumented individual but also the family as a whole because of the possibility of separation, economic hardship from deportation or detention, and adversity from discrimination. (70)

Growing evidence, mostly from observational studies, has shown an increased risk for different adverse health outcomes associated with political events and racial and ethnic discrimination, as well as anti-immigrant rhetoric. (71)(72)(73)(74)(75) For example, a cohort study of US-born Latino adolescent children of immigrant parents in California demonstrated that “perceived immigration policy vulnerability” was associated with increased anxiety levels, sleep problems, and blood pressure changes. (76) Research has mainly focused on the impact of an individual perception of stress and anxiety associated with undocumented or mixed-status families (members of these families are both US born as well as immigrants with different documentation status). We know much less about the potential intergenerational and transgenerational effects of children affected by the parental documentation status. (71)(77) Ethnicity-related stress or discrimination during pregnancy and its effect on infant outcomes, particularly on

low birthweight, were observed in a few studies in infants of mothers with Arabic names 6 months after the 9/11 terrorist attacks in the United States (72) and in Latina mothers after a major immigration raid. (73) More recently, a population-based study found an association between the US presidential election in 2016 and an increase in preterm births among US Latina women demonstrating the potential effects of “political determinants of health.” (74)(75) On the other hand, a recent study demonstrated that protecting unauthorized immigrant mothers had a positive effect on their children’s mental health. (77)

Evidence in this area continues to build. However, considerably less is known about the accompanying fear, anxiety, and acculturative stress of being an immigrant (both documented and undocumented), how to measure it, and how it affects health behaviors, particularly in this era of constant changes and awareness of immigration policies. More evidence is needed to understand severe types of adversity arising from deportation and family separation, as well as of immigration as part of a continuum of daily experiences that can contribute to psychosocial stress or resilience. Daily factors potentially associated with having a foreign-born status such as limited English proficiency, acculturation, low socioeconomic status, restricted access to health care and social services, immigration status, and perceived discrimination to name a few, have been only partially characterized. Further research will be necessary to understand how changes in immigration policy and applicant detention practices affect our children, their families, and their communities.

## Infant and Parental Stress in the NICU

Families of infants hospitalized in NICUs may experience high levels of both psychological and biological stress because of many aspects of admission, including separation, alterations in the parenting relationship, exposure to a technical and noisy environment, appearance of a small and fragile infant, need for multiple invasive procedures, uncertainty, financial burden, and prolonged hospitalization. (78)(79)

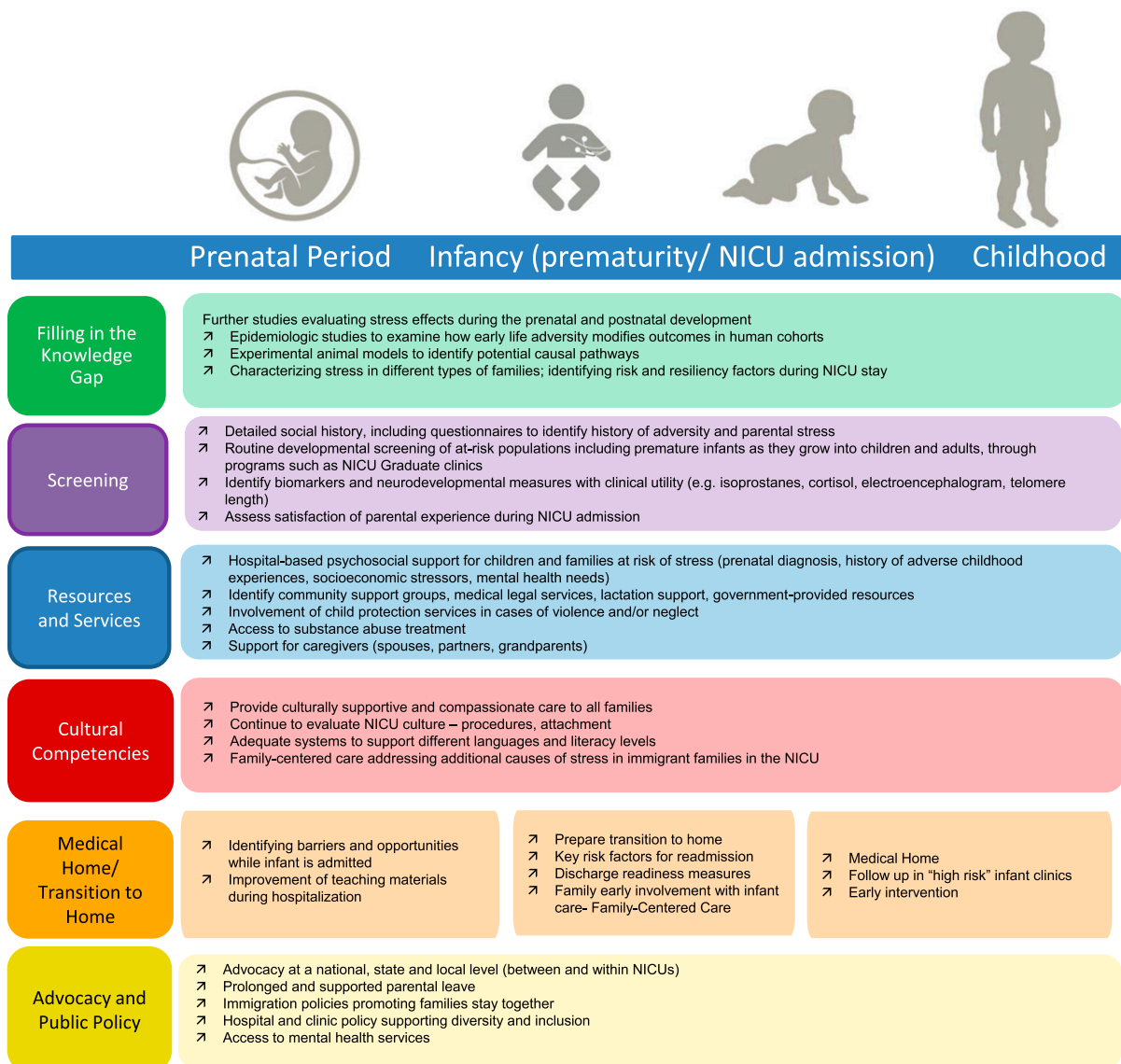
Many families with adverse experiences in the NICU and after their infant’s discharge have shared their stories in the lay press reporting high levels of stress, anxiety, depression, guilt, and shame. (80)(81) Several studies have replicated these findings among many different ethnic and cultural groups as well as in different countries. (82) A study conducted by the Bliss Foundation found that among 600 NICU parents surveyed in the United Kingdom, 23% were diagnosed with anxiety, 16% with post-traumatic stress disorder, and 14% with postnatal depression. (83) Among affected

parents, 45% reported no access to “formal psychological support” since leaving the NICU, (83) highlighting the importance of close multidisciplinary follow-up after NICU discharge.

Some studies have described the association between maternal anxiety in the NICU and later developmental outcomes in the offspring (eg, lower neurodevelopmental scores at age 20 months) (84); however, the available evidence makes it difficult to infer causation of neurodevelopmental delays because of maternal mental health problems (eg, depression, anxiety, and perinatal-specific post-traumatic stress), particularly in children with an increased

risk at baseline. A review of the mental health of parents in the NICU reports that mental health issues are common across diverse ethnocultural groups and countries. (82)

In addition to psychosocial stress, infants admitted to the NICU are subject to multiple lifesaving but painful and invasive procedures, (85) noise, (86) separation from parents, and altered parent-infant bonding. This is particularly true for extremely preterm infants (<28 weeks’ gestational age) who have a higher risk for neurodevelopmental delays. (87) Given the high co-occurrence of multiple stressors, the nature of the association among these stressors (psychosocial and biological) is important to study.



**Figure 2.** Implications of stress and potential interventions in the NICU. Images printed and modified with permission from Anne Berens. Copyright Registration Number / Date: VAu001275841 / 2016-07-07



## STRESS AND ADVERSITY DURING CHILDHOOD AS A CAUSE OF ADULT DISEASE

Toxic stress can play an important role in disrupting the architecture of the developing brain, and as a result, influence behavioral, educational, economic, and health outcomes later in life during adulthood and in later generations. (38) In 1998, the Adverse Childhood Experiences (ACE) Study demonstrated a linear and robust association between a mix of experiences that were considered as adverse during childhood and lifetime risk for certain illnesses and poor quality of life. Participants were asked about a number of experiences, including “physical, sexual, and emotional abuse; physical and emotional neglect; whether the mother was treated violently; household substance abuse; household mental illness; parental separation or divorce; and whether a household member had been incarcerated.” (25) Importantly, the more adverse experiences (counted as the number of experiences, not the degree of adversity) present in childhood, the higher the likelihood of outcomes such as higher risk of metabolic diseases, cancer, mood disorders, and premature mortality, as well as adverse social outcomes such as lower educational achievements in the future. (88)(89)(90)(91) ACE Study has added greatly to the evidence of the impact of toxic stress and early life adversity on the development of physical and mental impairments. (25) The implications of these findings have changed the way we think about adult disease and how many of the adult impairments can be seen as developmental disorders that begin early in life and persist for a lifetime. This may explain persistent health disparities in generations associated with poverty, maltreatment, and discrimination during childhood. Prevention efforts to change adult behavior can begin with reducing toxic stress during childhood. (26) A recent study assessing the cumulative risk and latent class approach to adverse childhood experiences showed that a different combination of adverse childhood experiences could have different risk on health outcomes. For example, a subgroup of children exposed to both parental mental illness and poverty showed a higher risk for special health-care needs compared with other groups, suggesting the importance of specific combinations and not only the number of adverse childhood experiences. (92)

## CONCLUSIONS AND FUTURE DIRECTIONS FOR THE NICU POPULATION

Adverse experiences and psychosocial stress have biologic implications for those who experience them as well as future generations. The effect of toxic stress starts in utero and

may last a lifetime. A better understanding of the biologic mechanisms as well as identifying methods for mitigating stressors and finding markers of resilience are important in the future to mitigate stress effects as early as possible.

The generational transmission of toxic stress and early life adversity play a potential role in the pathogenesis of health disparities, which highlights the importance of effective monitoring of significant risk factors. The infant born prematurely or with a medical condition that requires intervention and hospitalization in an intensive care unit setting is at a higher risk for neurodevelopmental delays, and exposure to additional stressors for both the infant and the parents. However, every system that interacts with children and their families offers an opportunity to influence and strengthen the foundation of a healthy development. Thus, having “extra” time during hospitalization and at least 3 to 5 years of additional outpatient monitoring in “high-risk infant clinics” or “infant follow-up clinics” can help identify children and families at risk for toxic stress. (38) Such monitoring can provide additional support for parents to adequately support the health and development of their infants. The use of traditional or novel biomarkers and physiologic measurements such as EEG to detect the early effects of adverse experiences in neonates will allow for improved identification of at-risk individuals. Such measures can also be used to assess the efficacy of bedside and home interventions to ameliorate the effects of stress faced by families and infants in the NICU (Fig 2).

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects of socioeconomic factors on the results and generalizability of outcome studies of NICU graduates.
- Know the effects of family risk factors (low socioeconomic status, mental health problems) on cognitive outcomes.
- Know the effects on the fetus and/or newborn infant of maternal psychiatric disorders and their treatment.

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# Renal Replacement Therapy in Neonates

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## Education Gaps

Acute kidney injury (AKI) represents an independent predictor of mortality in the NICU. Renal replacement therapy in the neonate presents the clinician with a unique set of challenges. It is important for clinicians to recognize the modes of renal replacement therapy at their disposal, appropriate indications for each modality, and the evolving technologies designed to overcome the limitations of renal replacement therapy in these patients.

## Abstract

Acute kidney injury (AKI) is a highly prevalent disease entity in the NICU, affecting nearly one-quarter of critically ill neonates by some reports. Though medical management remains the mainstay in the treatment of AKI, renal replacement therapy (RRT) is indicated when conservative measures are unable to maintain electrolytes, fluid balance, toxins, or waste products within a safe margin. Several modalities of RRT exist for use in neonatal populations, including peritoneal dialysis, hemodialysis, and continuous RRT. It is the aim of this review to introduce each of these RRT modalities, as well as to discuss their technical considerations, benefits, indications, contraindications, and complications.

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### ABBREVIATIONS

AKI	acute kidney injury
APD	automated peritoneal dialysis
CARPEDIEM	Cardiac and Renal Pediatric Dialysis Emergency
CAVH	continuous arteriovenous hemofiltration
CRRT	continuous renal replacement therapy
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
ECMO	extracorporeal membrane oxygenation
ELBW	extremely low birthweight
HD	hemodialysis
MPD	manual peritoneal dialysis
Nidus	Newcastle infant dialysis ultrafiltration system
PD	peritoneal dialysis
RRT	renal replacement therapy
UF	ultrafiltration
VLBW	very low birthweight

## Objectives After completing this article, readers should be able to:

1. Identify the indications for the initiation of renal replacement therapy in the neonate.
2. Summarize the basic mechanics of peritoneal dialysis, hemodialysis, and continuous renal replacement therapy.
3. Describe the complications of each mode of renal replacement therapy as they pertain to the neonate.

## INTRODUCTION

Acute kidney injury (AKI) is an independent predictor of morbidity and mortality in the NICU (1)(2) and affects 6% to 24% of critically ill neonates. (1)(3)(4)

Extremely low-birthweight (ELBW) and very-low-birthweight (VLBW) infants represent particularly high-risk groups. (1)(2)(5)(6) Though there has been disagreement regarding the strict definition of neonatal AKI in the past, increased attention to research in this field during recent years has led to standardized definitions that account for factors such as serum creatinine values, relative rise in serum creatinine, need for renal replacement therapy (RRT), and urine output. (7) AKI presents with a well-established clinical picture characterized by an abrupt decrease in renal function with variable presence of oliguria/anuria, edema, hypertension, and/or encephalopathy. (8) Common causes include sepsis, hypovolemia, respiratory distress syndrome, asphyxia, renal arterial/venous thrombosis, receipt of nephrotoxic medications, and congenital anomalies of the kidney and urinary tract. (9)(10) Although medical management remains the mainstay of therapy in the management of AKI, RRT is indicated when conservative therapy fails to adequately treat AKI and its complications (eg, metabolic acidosis, hyperkalemia, fluid overload, uremia with bleeding, or encephalopathy). (11)(12)(13) In the case of worsening fluid overload, prompt initiation of RRT is particularly important, because mortality is directly correlated with the degree of fluid overload at the time of dialysis initiation, and worsened outcomes are seen in those who do not receive convective RRT. (14) Additional indications for RRT include the need for the removal of dialyzable toxins, especially hyperammonemia in the case of inborn errors of metabolism. (13)

RRT can be implemented through various modalities including peritoneal dialysis (PD), intermittent hemodialysis (HD), and continuous RRT (CRRT). Several factors dictate the mode of RRT implemented: urgency of fluid/waste removal, hemodynamic stability of the patient, contraindications to a specific modality or access type, limitations based on the size or anatomy of the neonate, and resources available at a given institution.

It is the aim of this review to introduce each of these RRT modalities, as well as discuss their technical considerations, benefits, and complications.

## PERITONEAL DIALYSIS

PD is usually the preferential mode of RRT in neonates. Notable exceptions include the need for rapid fluid removal or rapid waste product clearance, as discussed in the sections on HD and CRRT later in this article. In PD, the vascular peritoneal lining serves as the dialysis membrane. Installation of hypertonic, electrolyte-containing dialysate

solution into the peritoneal cavity creates a transmembrane osmotic gradient that allows removal of fluid, termed ultrafiltration (UF). Solute clearance occurs through the diffusion of waste products down their concentration gradients. (15) Drainage of the fluid from the abdomen completes 1 cycle, which is then repeated at prescribed intervals. The result is gradual, continuous removal of solutes and fluid that helps to replace renal function. (13) The touted immediate advantages of PD over other forms of RRT include simplicity of operation, preservation of vascular access, and the ability to perform dialysis in children with hemodynamic instability. (12)(13)(16)(17) The more remote advantages of PD in children who may require long-term dialysis are decreased dietary restrictions, the ability to perform dialysis at home, and possible improved preservation of native kidney function compared with HD. (12)(16)(18)

## Technical Considerations

The Tenckhoff catheter (11 cm from proximal cuff to catheter tip) is the most commonly used catheter for intraperitoneal access. (19) However, its intraperitoneal length may be too long for use in small infants, leading to an increased tendency for catheter migration. In addition, it may be too wide for use in the neonate with sparse subcutaneous fat, causing pressure and resultant skin necrosis. Because of these considerations, the Flex-Neck catheter (7.5 cm from proximal cuff to catheter tip) or Cook acute peritoneal dialysis catheter (8 cm from cuff to catheter tip) are the preferred intraperitoneal catheters for neonates in some institutions. (20)(21) Considerations regarding the elements of catheters include the intraperitoneal configuration (curled vs straight), number of Dacron cuffs (single vs double), and a straight versus “swan-neck” subcutaneous tunnel configuration. Advantages of the curled catheter include decreased inflow pain, less catheter migration out of the pelvis, and less trauma to the bowel. (20)(22) Double-cuffed catheters have shown a longer time until first episode of peritonitis compared with single-cuffed catheter (23) as well as lower incidence of removal secondary to exit site or tunnel infection. (24) Swan-neck catheters have demonstrated lower rates of exit site/tunnel infections compared with straight catheters. (25) The placement of a PD catheter in a neonate must be such that the exit site is located outside the diaper region to prevent contaminations, with another consideration being that the exit site should, if possible, be placed on the side of the abdomen contralateral to any stoma (eg, vesicostomy, ureterostomy, colostomy, or gastrostomy). (16)

Certain risks exist with the initiation and ongoing performance of PD, including the potential for pericatheter



leakage, infection, and hernias secondary to increased intra-peritoneal pressure. (13)(20)(26) To minimize these risks, delayed initiation of PD with a dialysis-free period of 2 to 3 weeks after catheter insertion is advisable when possible, (20)(27) and once PD is started, low initial fill volumes (10 mL/kg or 200 mL/m<sup>2</sup>) (13)(16)(20) and shorter dwell time (30–50 min) (20) with gradual increase during the first weeks to fill volumes of 30 mL/kg or 800 mL/m<sup>2</sup> are recommended. (21)(28)

### Manual versus Automated PD

PD can be administered in 2 different methods: a manual gravity-based PD system or automated PD (APD). Manual PD (MPD) entails manual instillation of fresh dialysate and drainage of effluent and is reliant on gravity for fluid exchange into and out of the peritoneal cavity. (3)(29)(30) This method has the benefits of simple performance with limited cost of equipment, (30) as well as the capability to administer extremely low fill volumes, (13)(17) which can be pertinent in VLBW and ELBW infants. A closed, sterile system should be used to reduce infection risk. (21)(31) Commercially available systems include buretrols, which are essential for the strict and careful measurement of inflow and outflow volumes. (21) MPD is a labor-intensive process with 24 exchanges occurring daily upon initiation of dialysis, with a gradual decrease to as few as 8 exchanges per day in those patients requiring chronic MPD, and with each cycle lasting 30 to 120 minutes in duration. MPD requires close monitoring to ensure accurate dwell volumes and measurement of net UF. (29)

In contrast, APD uses automated machinery referred to as a “cycler” to perform continuous cycling PD. (3) In the neonate, this has multiple advantages compared with MPD, including a decreased need for constant monitoring because of programmable settings for dialysis delivery, shortened fill/drain times allowing more efficient dialysis cycling, and decreased rates of peritonitis. (29)(32)(33) The main disadvantage is its decreased ability to perform at fill volumes less than 60 to 100 mL. (13)(17)(20)(29)

### Nutritional Considerations

Among the many concerns facing infants requiring PD is adequate nutrition. A poor nutritional state can result in loose tissue texture and impaired wound healing, thereby increasing the risk of pericatheter leakage. (20) Factors that contribute to malnutrition in the infant receiving dialysis include loss of sodium in the ultrafiltrate, protein/amino acid losses to dialysis, loss of enteral nutrition because of vomiting, and reduced spontaneous intake because

of factors such as delayed gastric emptying. (20)(34) Adequate nutrition can be achieved in these patients through:

1. Sodium supplementation to compensate for losses into the ultrafiltrate (approximately 13 mEq [13 mmol] for every 100 mL of UF) (20)
2. Appropriate energy intake for adjusted chronologic age, taking into account that up to 10 kcal/kg per day may be obtained from dextrose within the dialysate (20)
3. Provision of appropriate dietary protein for ideal body weight (1.8 g/kg per day for infants receiving PD who are 0–6 months of age and 1.5 g/kg per day for patients 7–12 months of age). (35)

Provision of adequate nutrition often necessitates enteral supplementation via nasogastric or gastrostomy feedings. Adequate nutrition can result in normal or even catch-up growth, particularly in patients younger than 2 years. (34)

### Special Populations: VLBW and ELBW Infants

VLBW (birthweight <1,500 g) (1)(5) and ELBW (birthweight <1,000 g) (3)(36) infants are at particularly high risk for AKI because of factors such as infection and exposure to medications that may contribute to AKI, including indomethacin, aminoglycoside antibiotics, and loop diuretics. (1)(5)(36) When considering RRT, the small size of these infants presents unique challenges, including limited availability of appropriately sized dialysis catheters, limited access to machines approved for use in the neonate, and difficulties with catheter placement. (37) Given these considerations, various novel approaches to PD have been used to successfully provide dialysis to these infants (Table 1). The smallest commercially available PD catheters often remain too large for use in ELBW infants when placed infraumbilically and directed into the pelvis in the standard fashion. Harshman et al described successful administration of PD to an 830-g infant by inserting the dialysis catheter into the left upper quadrant with subsequent direction of the catheter to the pelvis. (37) Stojanović et al described the improvised use of intravenous cannulas and umbilical venous catheters for peritoneal access. (1) Of note, because of the extremely small dwell volumes, MPD rather than APD is used in ELBW and VLBW neonates. (3)

### Contraindications

Though PD is considered the modality of choice for neonatal RRT, there are situations when it is infeasible or inappropriate. Contraindications to PD include neonates with a diaphragmatic hernia, recent intra-abdominal surgery, an intra-abdominal malignancy, an inadequate peritoneal surface, and in some cases, necrotizing enterocolitis.

**TABLE 1. Outcomes and Complications of Peritoneal Dialysis in Extremely (ELBW) and Very (VLBW) Low-Birthweight Infants (74)**

PUBLICATION	AGE AT DIALYSIS START (DAYS)	BIRTHWEIGHT (g)	DIALYSIS DURATION	ACCESS METHOD	COMPLICATIONS	SURVIVAL
Stojanovic et al (3)	4	470	1 d	24G IV cannula	None reported	No
Macchini et al (75)	20–34	630–1097	3 d long-term	Straight Tenckhof-2, Broviac-1	Leak (2/3)	67% (2/3)
Yu et al (76)	6–32	630–1430	2–10 d	14G Arrow Vascath with manually added side-holes	Peritonitis-2, Leak-2, Hernia-1, Hemoperitoneum-1	10/16 survived to 60 days after dialysis
Sizun et al (77)	4–41	640–700	51–136 h	16G venous catheter or 20G chest tube	Leak, hyperglycemia, and PD catheter malfunction	None (3/3 survived dialysis but died of extrarenal causes)
Nakamura et al (78)	6.2 ± 5.2	701 ± 118	7.1 ± 6.9 d	10F J-VAC drain or Tenckhoff straight catheter	Leak, hyperglycemia, and PD catheter malfunction	9/14 weaned off PD; 3/14 survived to discharge
Kanarek et al (79)	3	710	30 h	Adult PD catheter cut down and flame-sealed	None	Yes
Harshman et al (37)	5	830	16 d	8.5F, 8-cm Cook PD catheter	Hypotension	Yes
Millner et al (80)	2	850	1 d	Trocar catheter "Vygon 0.8 cm"	Catheter malfunction	Yes
Rainey et al (81)	8	930	14 w	Tenckhoff PD catheter	Peritonitis, hernias, catheter malfunction	Yes

Frequently occurring themes include the importance of dialysis catheter choice and placement, high mortality (especially in patients with multiorgan disease), and the short-term nature of most reported courses of dialysis in extremely and very low birthweight infants. IV=intravenous; PD=peritoneal dialysis.

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(13) Although not a contraindication, PD should be used with caution in neonates with pulmonary compromise because increased intraperitoneal pressure has been correlated with poorer pulmonary function. (38)

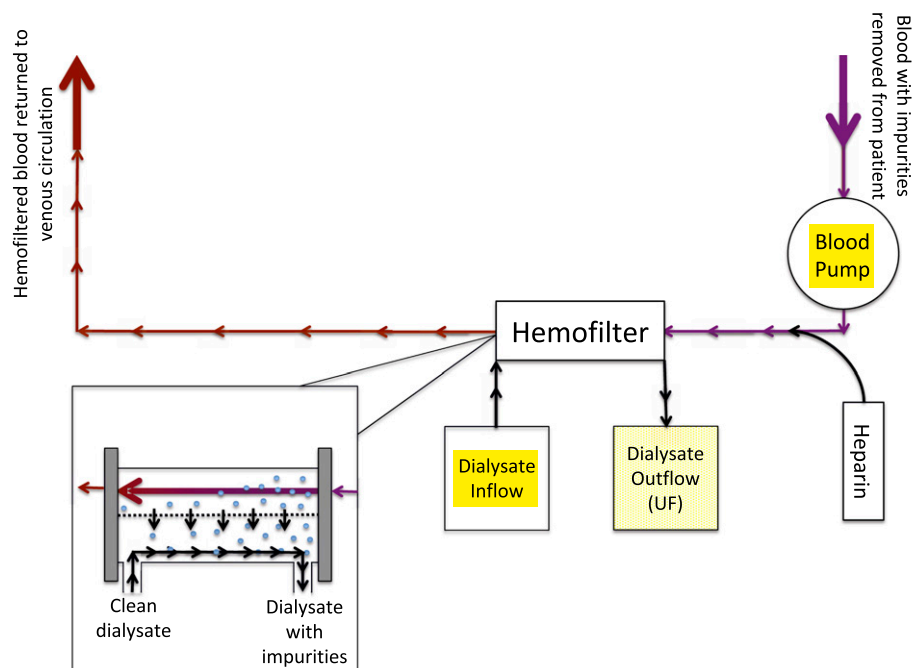
### Complications

With a 1-year mortality rate of approximately 7% in infants, (39) PD is not without risks. Mechanical complications include catheter obstruction by the omentum, catheter migration out of the pelvis, blockage of the catheter by fibrin or clots, bleeding with catheter insertion, and rarely, bowel perforation with catheter insertion. (16)(40) Other complications include hyperglycemia, hypoalbuminemia, peritonitis, and catheter exit site infection. (12)(40) Efforts to mitigate these complications have

included ensuring sterile technique; use of coiled, double-cuffed, swan-neck catheters (as described before) (20)(22)(23)(24)(25); and aggressive bowel regimens to prevent catheter migration and malfunction secondary to high fecal burden. (41)

### HEMODIALYSIS

In HD, blood passes through an HD filter, through which the dialysate solution runs in a countercurrent fashion across a semipermeable membrane before returning filtered blood to the body via venous access (Fig 1). By virtue of this countercurrent flow, a high concentration gradient of solutes is established between the blood and dialysate, allowing for efficient **diffusive clearance** (ie, removal of



**Figure 1.** Schematic of hemodialysis circuit. The dialysate and blood are run in a countercurrent fashion through the hemofilter to establish a diffusive gradient across a semipermeable membrane.

solutes by movement down their concentration gradients). The presence of positive pressure in the blood compartment of the hemofilter, coupled with negative suction applied to the dialysate compartment, facilitates a hydrostatic pressure gradient across the membrane (transmembrane pressure), which allows for fluid removal as well as some **convective clearance** (ie, removal of solute as it follows fluid across the membrane).

Although intermittent HD is the most efficient modality of dialysis, (13) multiple challenges exist in providing HD to the neonate. In addition to requiring continuous caregiver presence during HD sessions, usually necessitating a nurse-to-patient ratio of 1:1 or 2:1, (42) the equipment currently available is often too large for the neonate. Specifically, many circuits contain a relatively large extracorporeal volume (typically  $\geq 60$  mL) (13)(43) despite recommendations that extracorporeal blood volumes greater than 7% to 10% of the infant's blood volume should be avoided (**total blood volume approximated to 80 mL/kg in term infants and 100 mL/kg in premature infants**). Further, most HD machines have a UF error rate of  $\pm 50$  mL/h, which can generate significant errors in fluid balance in a small infant after a multihour dialysis session. (42) HD requires relatively rapid fluid and waste product removal compared with PD or CRRT. Finally, the necessary vascular access is often too large to reasonably be used in the neonate.

### Technical Considerations

When considering vascular access for HD, the minimum recommended catheter size is a **7F double lumen** (44); however, this may be difficult to achieve in small neonates. It has been suggested that rather than a double-lumen catheter, a short wider single-lumen catheter with a Y-connector present near the cannula may optimize blood flow by means of the Poiseuille law (resistance to flow through a tube is inversely proportional to the fourth power of its radius). (45) An additional consideration with the HD catheter is the use of a cuffed versus uncuffed catheter. Though both are effective forms of vascular access when providing HD, cuffed catheters have a longer median survival of 2 to 4 months (42)(46)(47) compared with 1 to 2 months with uncuffed catheters, (46) as well as a lower infection rate. (46) However, cuffed catheters do require more extensive surgery to insert and remove and are more susceptible to kinking and trauma compared with uncuffed catheters, such that **uncuffed catheters may still be preferable if only short-term access is anticipated**. (46)

Because catheter and circuit thrombosis is a risk for HD, anticoagulation needs to be implemented during its performance. This can be achieved using a **continuous heparin infusion (10–20 units/kg bolus followed by 10–30 units/kg per hour)**, or via a **single injection of low-molecular-weight heparin (0.5–1 mg/kg) at the initiation of the dialysis session**. In addition, to prevent thrombus of the catheter in the

interim between HD sessions, heparin (1,000–2,000 units/mL) should be instilled at the completion of each session. (42)

Infants are susceptible to significant electrolyte and fluid shifts early in HD initiation; therefore, it is advisable to start with low blood flow rates (3–5 mL/kg per minute) during initial sessions before gradually increasing to goal extracorporeal blood flow rates ( $16 \pm 5$  mL/kg per minute). (42)

### Complications

Survival in children receiving HD is generally the lowest in the youngest patient populations, with 1-year survival rates for those starting dialysis before age 1 year reported at 83% to 89%, and infection cited as a major cause of mortality. (48)(49) Many complications of HD are catheter-related, with the most common being catheter infection, migration, clotting, and kinking. (12)(46)(50) Intradialytic hypotension can occur in neonates because of an inability to tolerate rapid fluid shifts, which may present as pallor, emesis, irritability, drowsiness, diaphoresis, and occasionally seizures. (11)(13)(42) Infants receiving HD often demonstrate significant anemia, which may be secondary to considerable relative blood loss to the extracorporeal volume of the circuit, as well as dilutional in the setting of HD initiated for fluid overload.

A rare but dreaded complication of HD is the dialysis disequilibrium syndrome, in which patients experience neurologic deterioration, most typically during or immediately after the first HD treatment. (51)(52) It is hypothesized the dialysis disequilibrium syndrome results from cerebral edema secondary to osmotic shifts driven by a gradient of high urea in the cerebrospinal fluid compared with the dialyzed blood. (53) This mechanism has been further substantiated through uremic rat models, which have demonstrated increased cerebral edema, as well as a large urea gradient between the cerebrospinal fluid and blood after rapid HD. (54)(55) It is therefore recommended that the initial HD treatments have a lower clearance (Kt/V) goal for patients with high blood urea nitrogen levels.

### CONTINUOUS RENAL REPLACEMENT THERAPY

Since the 1980s, CRRT has served as a method of dialysis in neonates who are too hemodynamically unstable for PD or HD. (56) Initially, this was performed using continuous arteriovenous hemofiltration (CAVH), wherein a simple circuit was established by connecting a small hemofilter to an artery and a vein. (8) A hydrostatic pressure gradient, established by systemic blood pressures, would generate slow continuous UF with clearance largely being

accomplished via convection. (8) In the years that followed, a pump was added to the circuit with CRRT being accomplished by accessing 2 veins or a single vein with a double lumen catheter, thereby eliminating the need for arterial access. (8) This advancement permitted the performance of modern CRRT, which is divided into 3 types:

1. Continuous venovenous hemofiltration (CVVH), which achieves clearance principally using convection
2. Continuous venovenous HD (CVVHD) which uses dialysate to perform clearance via diffusion
3. Continuous venovenous hemodiafiltration (CVVHDF), which uses both convective and diffusive forces (8) (57)

Compared with CAVH, these methods of CRRT have the benefits of increased accuracy when monitoring fluid balance, increased automaticity of the circuit, and increased safety for patients. (8)

At present, most commercially available machines in the United States are approved for adults or older children weighing more than 15 to 20 kg, forcing off-label usage when clinicians implement CRRT in infants. (8)(58)(59) Among the challenges of current CRRT circuits is their relatively large extracorporeal volume, with the smallest available circuit currently in use in the United States being the Prismaflex M60 filter (Baxter International Inc., Deerfield, IL) with an extracorporeal volume of 93 mL that, even in the case of a full-term neonate, can be more than 25% of the patient's blood volume. (58)(59)(60) For cases in which the circuit volume is greater than 10% of the patient's blood volume, blood priming of the circuit has been advised to avoid acute hemorrhagic shock and to reduce overall morbidity. (58)(59) However, blood priming is not without its own risks, including acidosis, hypocalcemia due to calcium chelation by citrate-containing preservatives in blood, hyperkalemia, hypotension, and coagulopathy caused by the anticoagulant effects of citrate. (58)(59)(60)

In recent years, efforts have been made to develop CRRT filter sets with smaller extracorporeal volumes to minimize blood prime volumes and the associated risks; these include the Prismaflex HF20 membrane and Prisma M60 set, which have blood volumes of ~60 mL (61) and ~50 mL, (62) respectively, but neither of these is available in the United States. (58)

### Low Extracorporeal Volume CRRT Modalities

To address the previously mentioned difficulties in providing CRRT to neonates, European innovators have developed low extracorporeal volume CRRT circuits (Table 2), including the Cardiac and Renal Pediatric Dialysis

TABLE 2. **Comparison of Low Extracorporeal Volume Continuous Renal Replacement Therapy Modalities**

DIALYSIS CIRCUIT	PATIENT SIZE (kg)	EXTRACORPOREAL VOLUME (mL)	ACCESS REQUIREMENTS	ULTRAFILTRATION RATE (mL/h)	MODE OF CLEARANCE
Nidus	0.8-8.0	6.5	Single lumen	0-60	Diffusion
CARPEDIEM	2.0-9.9	27-45	Double lumen	150-300	Convection
Aqualex	<15 <sup>a</sup>	33	Double lumen	0-500	Convection

<sup>a</sup>Weights of patients included ranged from 2.7 to 12.4 kg. (59)

Emergency (CARPEDIEM™) (Bellco Medtronic, Mirandola, Italy) circuit, and the Newcastle infant dialysis ultrafiltration system (Nidus™) (Allmed, London, England).

CARPEDIEM was developed with the aim of creating a method of CRRT for **small and premature infants** with weights of 2.0 to 9.9 kg and estimated blood volumes ranging from less than 200 mL to 1,000 mL. (8)(63) This circuit has the benefits of small size—allowing it to be transportable—accurate blood-pump flow rates with flow errors of less than or equal to 7.5%, (43)(63) and minimal priming volumes. The CARPEDIEM has multiple available circuit configurations of different extracorporeal volumes (27 mL, 34 mL, and 45 mL) so that the circuit can be adjusted based on patient size. (58)(63) Despite achieving access using a smaller catheter than previously described (4–4.5F double-lumen catheter), blood pump flow rates of 5 to 50 mL/minute are achievable with UF up to 2.5–5 mL/minute (150–300 mL/h). (8)

Similar to the CARPEDIEM circuit, the Nidus machine is targeted for application in the neonate; however, it can be used even in ELBW/VLBW infants with a weight range of 800 g to 8 kg. (43) In addition, it offers an even smaller extracorporeal volume of 6.5 mL (58) and has the benefit of **self-priming with heparinized saline without the need for blood priming**, (43) thereby avoiding some of the blood prime–related complications discussed previously. The Nidus machine touts the further benefits of higher clearance compared with PD, UF of 0 to 1 mL/min (0–60 mL/h) with precise control of 0.25% difference between predicted and actual fluid removal weights at the end of treatment, and requirement of **only a single lumen access** with a 4F catheter. (43)(59)

Though originally designed for fluid removal in adults with heart failure unresponsive to diuretic therapy, the Aqualex™ machine for UF (CHF Solutions, Eden Prairie, MN) has been adapted by some centers in the United States for slow continuous UF and CVVH in small children. (59) Using

this circuit, UF rates of 0 to 500 mL/h can be achieved, and at this higher UF, clearance of waste products in small children via convection is reportedly possible with the simultaneous administration of electrolyte-balanced replacement fluids such as Prismaate™ (Baxter International Inc., Deerfield, IL). (59) Though the Aqualex is currently available and used in American markets, it remains a suboptimal means of RRT in infants compared with the CARPEDIEM and Nidus machines. The Aqualex™ has an extracorporeal volume of 33 mL, and requires a blood prime for small infants. (59) Because it was designed for slow continuous UF rather than CVVH, it does not have a built-in pump for replacement fluids, and issues can arise with the accuracy of prescribed versus actual UF and replacement fluid rates. In addition, like the CARPEDIEM, the Aqualex relies on convective forces for clearance and mandates double lumen access, in contrast to the Nidus, which uses diffusion and requires only a single lumen catheter. (43)(59)

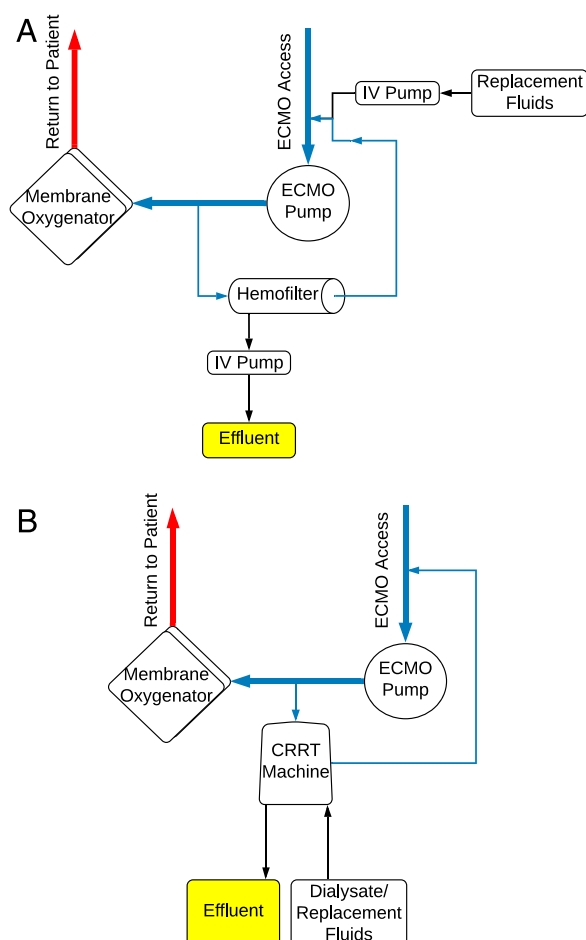
#### Use of CRRT in Conjunction with Extracorporeal Membrane Oxygenation

AKI represents a frequently encountered challenge in pediatric patients receiving extracorporeal membrane oxygenation (ECMO) support, with 1 study reporting AKI in more than 70% of pediatric cardiac patients receiving ECMO, with 58% of these receiving CRRT. (64) A complication in patients receiving ECMO that may necessitate CRRT therapy is **fluid overload** secondary to necessary replacement of blood products in critically ill patients, volume resuscitation, and third-spacing secondary to an exaggerated inflammatory response. (65) It has been reported that patients receiving CRRT in conjunction with ECMO therapy experience improved fluid balance with diminished need for diuretics compared with patients receiving standard ECMO without CRRT. (66) CRRT can be introduced into an ECMO circuit using either of

2 basic configurations: “filter-only” CRRT versus an “in-line” configuration (Fig 2).

Filter-only CRRT in which a hemofiltration filter is introduced into the ECMO circuit (Fig 2A) represents a common method to incorporate CRRT into ECMO therapy. (67) Using this form of CRRT, the hemofilter is connected after the ECMO pump, and UF is controlled via an intravenous infusion pump connected after the filter. (66)(67) This methodology has some advantages relative to adding a CRRT machine to the circuit (ie, an in-line configuration), including increased simplicity and lower cost. (66) However, filter-only CRRT in the setting of ECMO does run the risk of decreased control of pressures/blood flow through the hemofilter and a resultant decreased degree of accuracy in predicting UF relative to an in-line system. (68)

In contrast, an in-line configuration introduces a CRRT machine into the ECMO circuit (Fig 2B). Using this method,



**Figure 2.** A. Schematic of “filter only” continuous renal replacement therapy (CRRT) circuit in conjunction with extracorporeal membrane oxygenation (ECMO) circuit. B. Schematic of “in-line” CRRT circuit in conjunction with ECMO circuit.

a full CRRT machine is introduced after the ECMO pump. Advantages of this configuration include high, constant flow through the CRRT machine with the ability to perform clearance and UF in a controlled manner with minimal effect on the ECMO circuit. (67)

## Complications

As with other modalities of dialysis, CRRT has inherent risks. These include blood prime-associated risks (although priming the CRRT circuit with blood does reduce morbidity) such as **acidosis, hypocalcemia, hyperkalemia, thrombocytopenia, and coagulopathy.** (59)

An additional risk includes “bradykinin release syndrome” associated with hemofilters using an AN-69 membrane (including the M60 filter set). Blood samples from a blood bank used for circuit priming have been found to be acidotic, with a pH of 6.4. (69) It is hypothesized that contact of acidemic blood with the AN-69 membrane results in the generation of bradykinin, which in turn results in **tachycardia, hypotension, vasodilation, and anaphylaxis,** with some cases resulting in death. (69) Because of this potential risk, some centers have shifted from using the M60 filter set (extracorporeal volume 93 mL) to circuits using the HF1000 polysulfone membrane (extracorporeal volume 165 mL). (58)

## Hyperammonemia

Neonatal hyperammonemia represents a medical emergency that requires prompt intervention to minimize brain damage. Hyperammonemia can present as unexplained lethargy, feeding refusal, hypotonia, apnea, or seizures, with progression to coma and death within a matter of days. (70) The mainstays of therapy involve decreasing the production of ammonia through reversing catabolism and avoiding protein, as well as removal of toxic metabolites via dialysis. Some experts recommend rapid coordination of care among critical care, genetics, nephrology, and surgery/interventional radiology for ammonia levels **greater than 210 µg/dL** (150 µmol/L) to expedite effective treatment, with initiation of dialysis at ammonia levels **greater than 560 µg/dL** (400 µmol/L). (70)

Though the need for dialysis in the setting of neonatal hyperammonemia is uniformly agreed upon, the most appropriate modality is debated. Although PD is clearly insufficient to clear ammonia rapidly, (37)(71) HD and CRRT have been used effectively in the treatment of hyperammonemia. HD has the purported benefit of faster ammonia clearance relative to CRRT modalities, (72)



TABLE 3. Features of PD, HD, and CRRT

MODALITY	BENEFITS	DEFICITS	COMPLICATIONS	MODE OF CLEARANCE
PD	Simple to perform	Insufficient for rapid fluid/waste removal (eg, hyperammonemia)	Catheter migration	Diffusion
	Can be performed at home	Contraindicated if peritoneal membrane/cavity is compromised (eg, intra-abdominal surgery, congenital diaphragmatic hernia)	Catheter site infection	
	Fewer dietary restrictions relative to other modalities		Catheter tunnel infection	
	No vascular access No heparin requirement Can be used in patients with hemodynamic instability		Peritonitis Hyperglycemia Hypoalbuminemia Hyponatremia	
HD	Most efficient mode of clearance and UF	Large extracorporeal volume	Catheter migration	Diffusion and convection
		High margin of error in calculating UF	Catheter thrombosis	
		Requires continuous caregiver presence	Intradialytic hypotension	
		Requires vascular access Requires heparinized circuit Requires blood prime if extracorporeal volume exceeds 10% of patient blood volume	Dialysis disequilibrium syndrome Anemia Line infections	
CRRT	Can be used in patient with hemodynamic instability	Requires blood prime if extracorporeal volume exceeds 10% of patient blood volume	Line malfunction	Diffusion (CVHD, CWHDF)
	Able to use in conjunction with ECMO circuit	Requires vascular access	Line infections	Convection (CVH, CWHDF)
	Low extracorporeal volume modalities available (CARPEDIEM, Nidus, Aquadex)	Requires heparinized circuit	Line malfunction	

CARPEDIEM=Cardiac and Renal Pediatric Dialysis Emergency; CRRT=continuous renal replacement therapy; CVH=continuous venovenous hemofiltration; CVHD=continuous venovenous hemodialysis; CWHDF=continuous venovenous hemodiafiltration; ECMO=extracorporeal membrane oxygenation; HD=hemodialysis; NIDUS=Newcastle infant dialysis ultrafiltration system; PD=peritoneal dialysis; UF=ultrafiltration.

whereas CRRT carries the advantages of better hemodynamic stability and decreased risk of electrolyte imbalance compared with HD. (70)(71)(72) Of note, there have been conflicting reports on whether the rapidity of ammonia clearance once dialysis is started has any impact on prognosis of the disease. (72)(73) It is worth mentioning and emphasizing that prognosis has been shown to depend on the duration of patient coma preceding the start of dialysis. (72) With this in mind, the most important factor when deciding HD versus CRRT in the treatment of hyperammonemia should be which modality can be started in the most expeditious fashion in a given center. It is

advisable that physicians should have knowledge of the dialysis resources available at their centers, as well as an institutional protocol outlining the management of neonatal hyperammonemia to ensure that this metabolic emergency is recognized and treated in an expedient manner.

## SUMMARY

- AKI is prevalent among critically ill neonates. Though medical management is the mainstay of AKI treatment, RRT may be necessary when conservative measures fail.

Table 3 provides a comparison of the RRT options that are available in neonates.

- PD is typically the preferred modality of RRT in neonates. Immediate benefits of PD over other modalities of RRT include simplicity of operation and preservation of vascular access. Long-term advantages include decreased dietary restrictions compared with other modes of dialysis, and the ability to perform PD at home. PD is an insufficient mode of dialysis in certain circumstances when rapid removal of fluid or solute is needed.
- Intermittent HD is the most efficient mode of dialysis. However, multiple challenges exist in providing HD to the neonate (eg, relatively **large extracorporeal circuit volume**, **high error rate in calculating UF**, **rapid fluid/electrolyte shifts** creating potential for hemodynamic instability), thereby limiting its use relative to PD and CRRT in neonatal populations.
- CRRT is a mode of dialysis that can be implemented in patients too hemodynamically unstable to undergo PD or HD. CRRT can be readily used in patients requiring ECMO support. Among the challenges of neonatal CRRT is the **relatively large extracorporeal volume** of most currently available CRRT circuits. Recently, CRRT circuits with low extracorporeal volume have been developed for use in the neonate.
- Neonatal hyperammonemia is a medical emergency that requires prompt collaborative intervention among critical care, genetics, nephrology, and surgery/interventional radiology teams to halt/prevent brain damage. Although PD is insufficient to provide rapid clearance of ammonia, HD and CRRT have been successfully used in the treatment of neonatal hyperammonemia. Institutional protocols should be in place regarding the management of neonatal hyperammonemia to ensure expeditious treatment.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causes of renal failure in the neonate.
- Know the management of renal failure in the neonate, including indications for and complications of the use of hemofiltration, peritoneal dialysis, and hemodialysis.

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## NeoReviews Quiz

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1. Acute kidney injury (AKI) occurs in 6% to 24% of critically ill neonates and typically presents with oliguria or anuria, edema, hypertension, with or without encephalopathy. In situations in which medical management fails, renal replacement therapy (RRT) may be indicated. Which of the following findings does not represent a typical indication for RRT in a patient with AKI?
  - A. Hyperkalemia.
  - B. Severe fluid overload.
  - C. Hyponatremia.
  - D. Uremia with encephalopathy.
  - E. Metabolic acidosis.
2. Peritoneal dialysis (PD) is the primary method for RRT in neonates and infants. During PD, solutes are gradually removed by infusing a hypertonic electrolyte-containing solution in the peritoneal cavity, resulting in a transmembrane osmotic gradient and ultrafiltration. Which of the following statements regarding PD is correct?
  - A. Automated PD requires fill volumes of at least 150 mL.
  - B. To decrease the risk of leakage, infection, and hernias, a delay of 2–3 weeks after catheter insertion is recommended.
  - C. The 1-year mortality for infants requiring PD is 50%.
  - D. Infants receiving PD have stricter dietary restriction than those receiving hemodialysis.
  - E. Straight PD catheters have decreased inflow pain compared with curled catheters.
3. Malnutrition in infants requiring PD can lead to complications including pericatheter leakage from poor wound healing. Therefore, it is critical to optimize the nutritional status of these patients. Which of the following statements regarding nutritional considerations for infants requiring PD is correct?
  - A. Delayed gastric emptying and vomiting are rare and do not contribute to malnutrition in this patient population.
  - B. Sodium supplementation of 4 to 6 mEq (4–6 mmol) per 100 mL of ultrafiltrate is required to account for losses.
  - C. Calories from dextrose in the dialysate amount to up to 20 kcal/kg per day.
  - D. The recommended protein intake is 1.8 g/kg per day for infants aged 0 to 6 months.
  - E. With close attention to nutrition, the need for supplementation with a nasogastric or gastrostomy tube is uncommon.
4. Hemodialysis (HD) is the most efficient mode of dialysis. In HD, the blood runs through a filter and countercurrent to the dialysate resulting in removal of solutes via both diffusive and convective clearance. Which of the following statements regarding the use of HD in infants and neonates is correct?
  - A. Blood flow rates of 3 to 5 mL/kg per min are recommended when initiating HD.
  - B. HD can be achieved via a 3F double-lumen catheter.
  - C. Extracorporeal blood volumes greater than 20% should be avoided.
  - D. Most HD machines have an ultrafiltration error rate of  $\pm 25$  mL/h.
  - E. Dialysis disequilibrium syndrome is a common complication of HD in this population.

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5. Neonatal hyperammonemia is a medical emergency in which removal of toxic metabolites via dialysis may be necessary. Which of the following statements regarding the use of dialysis in the setting of hyperammonemia is correct?
- A. Rapid coordination of care, including consideration of transfer to centers capable of providing dialysis, can be initiated when ammonia levels rise above 560  $\mu\text{g/dL}$  (400  $\mu\text{mol/L}$ ), with cautious observation recommended for lower levels.
  - B. Initiation of dialysis can be withheld until ammonia levels rise above 1,000  $\mu\text{g/dL}$  (714  $\mu\text{mol/L}$ ).
  - C. Ammonia clearance is fastest with continuous RRT (CRRT) compared with HD.
  - D. The risk of electrolyte imbalance is decreased in HD compared with CRRT.
  - E. The duration of coma before the initiation of dialysis has been shown to have a significant impact on prognosis.



# Evaluation and Long-term Management of Neurogenic Bladder in Spinal Dysraphism

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## Education Gaps

The evaluation and management of neurogenic bladder in patients with spinal dysraphism is a lifelong endeavor that evolves in time; the top priorities of management include renal preservation and quality of life. Clinicians should be aware of the great barriers that patients face as they transition from pediatric to adult care.

## Abstract

Spinal dysraphism, which includes conditions such as myelomeningocele and sacral agenesis, is one of the most common causes of congenital lower urinary tract dysfunction. Early evaluation of the neurogenic bladder serves to minimize renal damage, and the main goals of management include preserving renal function, achieving acceptable continence, and optimizing quality of life. The survival of patients with such conditions has improved to greater than 80% reaching adulthood, owing to advances in diagnostic and therapeutic modalities. The result is a real, and unfortunately often unmet, need for successful transitional care in this complex patient population. Clinicians must be able to identify the unique challenges encountered by patients with neurogenic bladder as they shift through different stages of their life.

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### ABBREVIATIONS

BMI	body mass index
CDC	Centers for Disease Control and Prevention
CIC	clean intermittent catheterization
DMSA	dimercaptosuccinic acid
MMC	myelomeningocele
MOMS	Management of Myelomeningocele Study
QOL	quality of life
RBUS	renal and bladder ultrasonography
SA	sacral agenesis
SB	spina bifida
UDS	urodynamic study
UTI	urinary tract infection
VCUG	voiding cystourethrography
VPS	ventriculoperitoneal shunt
VUR	vesicoureteral reflux

## Objectives After completing this article, readers should be able to:

1. Summarize the early evaluation surveillance strategies and the assessment of renal function for lower urinary tract dysfunction
2. Explain the medical and surgical management algorithms for neurogenic bladder and how these can evolve as patients age
3. Describe the mainstay urologic goals in the management of neurogenic bladder in patients with spinal dysraphism: preserving renal function, achieving acceptable continence, and optimizing quality of life

4. Identify specific patient and clinician barriers to transitioning pediatric urologic care to adult physicians in this complex patient population
5. Identify urologic causes of morbidity in adult patients with spina bifida

## INTRODUCTION

Spinal dysraphism is a general, expansive term referring to the group of congenital spine and spinal cord defects derived from the anomalous development of ectodermal, mesodermal, and neuroectodermal tissues. This umbrella term includes conditions such as spina bifida (SB) occulta, meningocele, myelomeningocele (MMC), lipomyelomeningocele, and sacral agenesis (SA). (1) By far, MMC is the most common of these conditions that affect the bladder. MMC is characterized by the extrusion of the spinal cord into a sac filled with cerebrospinal fluid and most commonly affects the lumbosacral region. (2) SA refers to the absence of part or all of 2 or more sacral vertebral bodies and is rare. Although MMC is more easily identifiable on physical examination, a diagnosis of SA may be missed initially, because physical signs can be subtle. SA may be noted only on careful evaluation of a toddler with delayed toilet training or a urinary tract infection (UTI). (3) Disease manifestations of all spinal dysraphic conditions can be extremely variable, but sequelae often involve bladder, bowel, cognitive, and neuromusculoskeletal symptoms. (1)(4)(5) In this discussion, we will focus on the urologic evaluation and management of neurogenic bladder associated with SB, MMC, and SA.

## EPIDEMIOLOGY

The worldwide incidence of spinal dysraphism has declined since the 1970s, but the prevalence of the disease has been stable from 1997 to 2009. (6)(7)(8) According to the Centers for Disease Control and Prevention (CDC), about 1,645 infants are born with spinal dysraphism in the United States annually, with a prevalence of 3.17 per 10,000 live births. (9) Lloyd et al examined the Kids' Inpatient Database and noted a higher prevalence of SB in Hispanic newborns and a lower prevalence of SB in black and Asian newborns compared with the general population. (8) Survival rates for infants born with SB have improved significantly over the past century with enhanced methods of evaluation and management, including ventriculoperitoneal shunting (VPS), clean intermittent catheterization (CIC), and the use of antibiotics, which allow patients to achieve a normal lifespan. Twice as

many US newborns with SB survived in 1995 compared with 1975 rates, with 85% to 90% of affected children currently surviving into adulthood. (10) In contrast to SB, SA is rare, occurring in approximately 0.4 per 10,000 live births. (3)(11) The association of SA with maternal diabetes mellitus is well-known. (11) SA is part of the spectrum of caudal regression syndrome and may occur in isolation or be associated with Currarino syndrome (partial sacral agenesis, presacral mass, and anal atresia). (12)(13)

## MANAGEMENT GOALS

Currently, approximately 25,000 US children up to 19 years of age are affected by SB. (14) Owing to its rarity, the prevalence of SA in the United States is less known, but from a urologic perspective, this entity is important to identify because up to 80% of patients with SA have a neurogenic bladder. (3) For patients with SB and SA alike, the primary goals in management of the neurogenic bladder are preserving renal function, achieving acceptable continence, and improving quality of life (QOL).

Although imaging and laboratory data provide objective measures to assess renal preservation, defining and assessing continence can be both subjective and variable. The International Children's Continence Society recently published an update on the standardization of terminology for lower urinary tract function in the pediatric population for just this reason, and they define incontinence as "involuntary leakage of urine." (15) Across the literature, definitions can be vague and do not quantify the amount of leakage. For example, in a review assessing the standardization of definitions used for urinary incontinence in children with SB, Lloyd et al found that just over half of the 105 included articles defined what they considered to be "continent." No consensus exists on the objective measures of continence. For instance, even though the description of "always dry" was used most commonly among all included studies, this was consistent in only 24% of the 105 studies. (16) Continence is typically addressed as a child reaches school age because of social concerns, and the evaluation and management of reflux, bladder storage pressures, and the presence of UTIs are continuously addressed to optimize renal function.

QOL can be greatly influenced by patient variables such as the presence of a VPS. Ramachandra et al examined

health status and demographics as potential factors in health-related QOL using parent- and patient-reported questionnaires. (4) The authors concluded that shunted hydrocephalus had a negative impact on patients' perception of QOL, though the effect was attenuated by age. Other authors have identified that a higher level of the spinal lesion and the number of shunt revisions were associated with lower QOL. They also found that more shunt revisions were associated with lower mathematics skills and QOL, though causal relationships were yet to be determined. (17)

For patients with SB and SA, management can be complex, is multimodal, and evolves throughout a child's lifetime. As pediatric patients become older, they encounter new challenges, including the need to transition to adult clinicians, and research highlights that only half of adolescents and young adults are formally and properly prepared for the transition. (10) Increased hospital admissions during these later years may be attributed, in part, to this breakdown in the transition in health care; researchers are finding it increasingly important to establish a dedicated framework for patients to continue undergoing regular surveillance. (10)(18)

## PRENATAL DIAGNOSIS

Prenatal screening for spinal dysraphism is based on ultrasonography and maternal  $\alpha$ -fetoprotein screening as early as the first trimester. Although ultrasonography may detect up to 90% of MMC cases prenatally, a significant proportion of patients with some degree of SA are detected only after delivery, often in the evaluation of other associated anomalies or at the time of attempting toilet training. For instance, Cho et al found that in a cohort of 43 patients with SA treated for urologic conditions between 1981 and 2014, only 5 were diagnosed prenatally. (3) In this section, we will focus on the prenatal diagnosis of MMC and on in utero treatment outcomes.

Sequential in utero imaging in fetuses with MMC suggests that insults to both the central and peripheral nervous systems may be progressive throughout gestation. (2) At birth, damage to the spinal cord and the peripheral nerves is usually irreversible despite early postnatal repair. Animal studies have shown that prenatal coverage of SB-like lesions preserved neurologic function and decreased the degree of hindbrain herniation, supporting the hypothesis that in addition to the failure of neural tube formation, prolonged exposure of neural elements to chemical and mechanical trauma contributes to spinal cord injury and in turn, neurologic deficits. (19)(20) Children with MMC almost invariably have an associated Chiari II hindbrain malformation which is the principal cause of death. (21) Early data in human prenatal MMC repair suggest less hindbrain herniation and a lower than expected incidence of Chiari II

malformation compared with historic controls but also showed increased maternal and fetal risks, as outlined later in this article. (21)(22) Given these findings and that survivors usually have major neurologic disabilities, the Management of Myelomeningocele Study (MOMS) was performed to compare the efficacy of prenatal repair of MMC with that of standard postnatal repair. (2)

## Management of Myelomeningocele Study

In the MOMS trial, eligible pregnant women with a fetal diagnosis of MMC were randomly assigned to undergo either prenatal surgical closure before 26 weeks of gestation or standard postnatal repair. (2) The study's primary outcome (fetal or neonatal death, or the need for a cerebrospinal fluid shunt by 12 months of age) was reduced in the prenatal surgery group compared with the postnatal surgery group (68% vs 98%). Forty percent of patients in the prenatal surgery group required shunts in contrast to 82% in the postnatal surgery group (relative risk 0.48,  $P < .001$ ). The trial was stopped for efficacy of prenatal surgery, based on the results of 158 patients who were evaluated at 12 months of age.

Prenatal surgery also led to improved composite scores for cognitive and motor function at 30 months of age, decreased hindbrain herniation by 12 months, and ambulation by 30 months of age. However, intrauterine closure was associated with a significant increase in preterm birth (79% vs 15%), and uterine dehiscence occurred in 10% of women in the intervention group. The average gestational age was 34.1 weeks in the prenatal surgery cohort compared with 37.3 weeks in the postnatal surgery group. In addition, the group that received intrauterine surgery required more procedures for spinal cord tethering. Thus, while prenatal closure seemed to improve neuromotor development and decreased the need for a shunt, it came at the expense of serious potential risk to the pregnant woman and fetus. (2) When accounting for the complete cohort of 183 randomized patients, 30-month outcomes confirmed that prenatal repair improved the primary outcome composite score of mental development and motor function ( $P = .004$ ). Independent ambulation was also improved in the prenatal surgery group (44.8% vs 23.9%,  $P = .004$ ). (23)

## Urologic Outcomes after Prenatal Closure

Before the MOMS trial, Holmes and colleagues noted that fetuses with MMC undergoing prenatal surgery showed the same changes on video urodynamic studies (UDS) as children with MMC who underwent postnatal closure. (24) At 1 month, video UDS showed decreased bladder capacity, increased bladder storage pressures, and significant postvoid residuals in 4 of 6 patients who had intrauterine

surgery, similar to the outcomes reported with postnatal surgery. Hydronephrosis and vesicoureteral reflux (VUR) were seen in 4 and 3 patients who had prenatal closure, respectively. Thus, the authors concluded that prenatal surgical patients seemed to have the same urodynamic changes as patients who underwent postnatal closure based on historical data. In a larger cohort of 23 patients, Holzbeierlein and colleagues found that at 6.5 months, there was no difference in urodynamic parameters between the 2 groups. (25) Thirty-four percent of patients with prenatal surgery had decreased bladder capacity, 13% had detrusor overactivity, and 82% had a detrusor leak point pressure of greater than 40 cm H<sub>2</sub>O. At the same MOMS center, a longer follow-up of 9.6 years showed that this prenatally treated group had decreased bladder capacity in 71%, detrusor overactivity in 35%, and increased detrusor pressures in 25%. (26) The authors found that the timing of surgery (ie, pre- vs post-delivery) did not alter bladder management, need for urinary tract surgery, or UDS results in patients who were matched by age and sex. (26)

On the other hand, while the MMC cohort sizes were small, at 8 patients each, Horst and colleagues found that half of the 8 patients (50%) who had prenatal closure had neurogenic bladder dysfunction requiring CIC and anticholinergics compared with all of those (100%) in the postnatal surgery group. (27) Bladder wall thickening was noted to be higher in the postnatal closure group at 87.5% versus 37.5% in the prenatal group. Finally, febrile UTIs were more common in the postnatal group, occurring in 62% versus 37.5% in the prenatal group. However, long-term outcomes were not established with median 2-year follow-up in the prenatal group versus 4 years in the postnatal group. (27)

Post-trial analyses were performed on the MOMS cohorts to assess the impact on urologic function. Prenatal closure did not significantly reduce the need for CIC by age 30 months. However, prenatal surgery was associated with significantly less VUR, an open and thus incontinent bladder neck, bladder trabeculation, and ureteral dilation, and affected patients also had significantly better bladder shape. Further analysis in the MOMS II follow-up study is pending and is expected to reveal the impact on urinary continence and the need for CIC by school age. (20) Given the current data, children who have prenatal surgery still warrant close follow-up, similar to those who have undergone postnatal closure.

### Neonatal Evaluation and Management

The prevention of renal damage by ensuring safe bladder storage pressures and adequate bladder emptying at low pressures is the focus of postnatal urologic management. These issues need to be recognized and managed as early as

possible. However, evaluating the urinary tract and bladder function of neonates with MMC is not a priority because the initial focus of treatment is spinal closure and monitoring the infant's neurologic status. The timing and interpretation of UDS, the initiation of CIC, and other interventions are debated in the literature. (28) In addition, patients with SA may only be diagnosed later in the neonatal period when they have other abnormalities that warrant evaluation and provide clues to the clinician about the diagnosis. Unfortunately, the level of the spinal injury does not necessarily predict the degree or type of lower urinary tract dysfunction. (3) Thus, patients with MMC or SA should undergo an evaluation with renal and bladder ultrasonography (RBUS) and early determination of postvoid residual urine. The use of early functional imaging can detect damage to the upper urinary tracts that may not otherwise be readily identified during follow-up. In our practice, we initiate CIC in the neonatal period when there is evidence of significant postvoid residuals, severe bilateral hydronephrosis on RBUS, recurrent UTIs, or renal damage noted on functional imaging.

### Early Evaluation and Surveillance

A thorough urologic evaluation in patients with SB and SA includes RBUS, voiding cystourethrography (VCUG), functional imaging such as a radionuclide scan, and UDS, once feasible. These studies help to establish a baseline appearance and function of the upper and lower urinary tracts for future comparison, as well as to detect early signs of upper tract deterioration to prevent significant renal damage. (28) The timing of these initial studies can be controversial. Ideally, the affected patient should undergo RBUS soon after birth, and if there is evidence of hydronephrosis, ureteral dilation, renal size discrepancy, or bladder wall thickening, VCUG should be performed once medically possible. (29) In patients with SA, UDS is recommended at the time of diagnosis because bladder dysfunction cannot be predicted from neurologic abnormalities and it is important to identify those children at risk for renal injury. (30) These diagnostic tests help clinicians determine the need for antibiotic prophylaxis in the context of VUR or high-grade hydronephrosis. In patients with SB, we obtain UDS and a dimercaptosuccinic acid (DMSA) renal scan within the first 6 to 12 months of age. Patients with SB are followed in our multidisciplinary clinic, where serial RBUS is performed every 3 to 6 months for the first 2 years of age. Clinical changes or a change in the RBUS findings (eg, new or worsening hydronephrosis, renal asymmetry) prompts a repeat UDS, VCUG, and/or DMSA. The use of DMSA scans early in life has been instrumental in providing a baseline study for comparison that helps direct patient care based on actual renal functional loss or scarring.

Studies have shown various urodynamic changes in infants with SB. These include decreased bladder capacity, decreased compliance, detrusor overactivity, detrusor-sphincter dyssynergia, bladder outlet obstruction, and complete denervation. Because patients with MMC undergo spinal closure at an early age, research studying urodynamics in this population is typically carried out only after surgery is already performed. Kaefer and colleagues assessed 36 infants with MMC and found that patients with detrusor external sphincter dyssynergia had a higher risk for renal deterioration compared to those without dyssynergia (72% vs 11%). However, radionuclide scans to determine renal function were not included. (31) On the other hand, Shiroyanagi et al reported that while 25% of their cohort of 64 patients had abnormal DMSA scans, there was no significant difference in UDS findings of detrusor leak-point pressure and compliance among those with normal and abnormal DMSA scans. (32)

## EARLY MANAGEMENT STRATEGIES

There are 2 main schools of thought about neonatal bladder management: expectant versus proactive management. In expectant management, patients are monitored clinically with RBUS every 6 months until 2 years of age based on the recommendations of the International Children's Continence Society. (29) In this approach, CIC or UDS is only performed if the patient has a clinical deterioration (eg, new or worsening hydronephrosis or VUR, increased postvoid residual volumes, worsening renal function, or development of a UTI) or new renal ultrasound abnormalities. (28) Proponents of a more proactive approach initiate CIC early in the neonatal period, with or without anticholinergics, based on UDS findings. UDS is performed annually once patients are medically stable and recover from neurosurgical closure or if radiographic or clinical signs indicate significant change. Early studies and CIC are aimed at identifying patients with unsafe bladder parameters so that intervention can be undertaken before upper tract damage ensues. In some situations, a vesicostomy is needed to temporize further renal damage in patients with high-grade VUR and hydronephrosis.

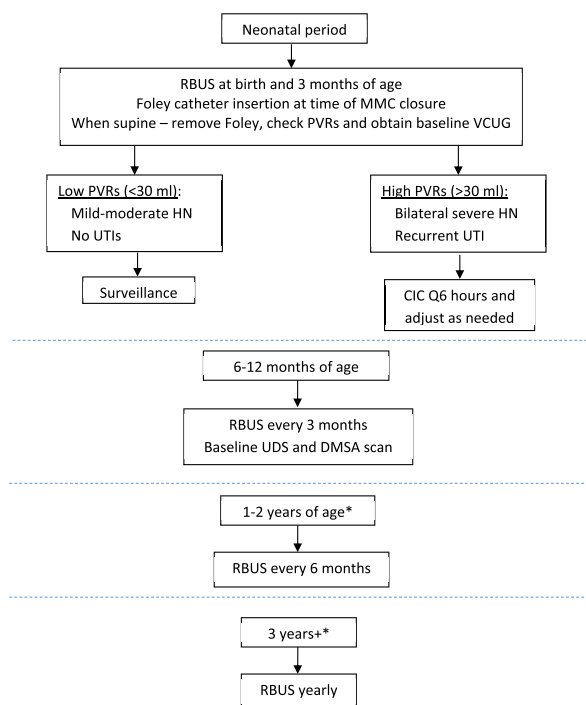
There is ongoing debate as to which approach should be taken, as evidenced by the British Association of Pediatric Urologists' consensus statement in 2016, which found half of its members in favor of early CIC for all patients while half were in favor of expectant management. (33)(34) Part of the controversy about the ideal management approach stems from inconsistent results in the literature. Teichman et al found a 5% rate of renal deterioration in patients who

received expectant management, which was statistically associated with UTIs and VUR; however, the renal deterioration that occurred was similar among patients with normal and abnormal UDS, implying that renal deterioration was not predicted by UDS. (35) In addition, Woo and colleagues found that the early CIC approach was associated with an increased incidence in abnormalities found on DMSA scans, suggesting that this strategy did not seem to prevent renal damage. (36) In contrast, other studies found that this proactive approach was associated with a decreased incidence of renal deterioration, which was defined as worsening hydronephrosis, worsening VUR, or increasing postvoid residuals. (37) In their expectant management group, 80% had upper tract changes and 14% went on to reconstructive surgery. Wu and colleagues similarly found increased augmentation rates in their expectant management group (27% vs 11%), but renal function or damage was not measured. (38) A more contemporary study performed by Elzeneini et al compared a cohort of patients with SB who were treated with CIC soon after birth to a historical cohort that received expectant management to determine if early catheterization was associated with a decrease in renal scar rate based on DMSA scans. (33) The mean follow-up was 11.4 years, and DMSA scans found renal scarring in 18.8% of the early CIC group compared with 39% in the expectant management group, with scarring occurring later in life in the early CIC group (47% vs 72% detected at 4 years of age). The authors concluded that early catheterization was renal-protective and recommended proactive management in all patients with SB.

Given the mixed outcome measures described by different authors, neither approach has emerged as the gold standard. In our practice, patients undergo catheterization during the initial closure of the spinal defect until they can be placed supine, and then bladder emptying is assessed. Infants with adequately emptying bladders are followed with baseline VCUG and ultrasound examination at birth and then UDS and DMSA within the first 6 to 12 months of age. In patients demonstrating urinary retention in the neonatal period, bilateral severe hydronephrosis, or recurrent UTIs, CIC is initiated and continued. Serial ultrasound examinations are performed every 3 to 6 months at our multidisciplinary spinal defects clinic up to 2 years of age and then yearly thereafter. Clinical changes or a change in the ultrasound examination prompts repeat UDS, VCUG, or a DMSA scan (Fig).

In 2012, the CDC organized a working group of pediatric urologists, nephrologists, epidemiologists, methodologists, community advocates, and CDC personnel to develop an approach to optimize the urologic management of children with SB from the newborn period to 5 years of age. (39) Efforts





**Figure.** Early bladder management and surveillance protocol of infants with spinal defect. \*Clinical changes, worsening HN prompts repeat UDS, VCUG, and/or DMSA scan. CIC=clean intermittent catheterization; DMSA=dimercaptosuccinic acid; HN=hydronephrosis; MMC=myelomeningocele; PVR=postvoid residual; RBUS=renal and bladder ultrasonography; UDS=urodynamics; UTI=urinary tract infection; VCUG=voiding cystourethrography.

are under way to study outcomes of standardizing the approach. Recruitment for the 5-year study began in 2015 and is ongoing. The protocol, outlined in Table 1, aims to address the current inconsistencies in outcomes reporting.

### Toddler to School Age

Renal preservation is a prevailing focus of urologic management in patients with SB, but with age, new management concepts are introduced. In the toddler to early school-aged child, bladder and bowel continence becomes a focus. Annual and as-needed RBUS, in addition to annual kidney, ureter, and bladder radiography, are recommended to assess the upper tracts and stool burden. In addition to neurogenic bladder, patients with SB can also have concomitant neurogenic bowel which can in turn affect the bladder's ability to effectively empty and is a risk factor for UTIs. Renal function is typically assessed with serum creatinine, though in more recent years, researchers have proposed cystatin C–based glomerular filtration rate as a more sensitive marker for detecting early chronic kidney disease in patients with MMC who have poor muscle mass. (40) In those children who fail to achieve toilet training, have changes on the RBUS,

have worsening incontinence, or have UTIs, repeating the VCUG, UDS, and a DMSA scan may be considered because bladder function and VUR are not static. Close monitoring of bladder function is particularly important during the first 6 years of age and during puberty, because changes are most pronounced during these periods. (41) Rapid growth during these periods can cause tethering (or retethering) of the spinal cord, which in turn can present as neurologic deterioration and worsening urodynamic parameters that place the kidneys at risk. (28)

Management options for urinary continence are summarized in Table 2. (42) If the affected child previously had safe urinary storage parameters without evidence of renal deterioration, and thus CIC has not been implemented, CIC should be started once failure to toilet train is recognized. An individual's CIC regimen is tailored to maintain continence as the child progresses to school age and occurs between 3 to 5 years of age. Anticholinergics are routinely used in conjunction with CIC and can help improve continence. If continence is still not yet achieved to the satisfaction of the patient/family, escalation of therapy with intravesical botulinum toxin injections with or without the use of a bulking agent injected at the bladder neck can be offered. (43) Finally, surgical reconstruction can be entertained during the school-age years. Several types of reconstruction options exist, including augmentation cystoplasty (to increase storage capacity), creation of catheterizable channels (to assist with the ease and compliance of catheterization in patients with reduced ability to perform CIC per urethra), and increasing outlet resistance. (42) Historically, reconstruction is usually reserved for early adolescence as patients gain more independence, but patient body habitus may support an earlier date for surgery. Donovan et al found that 33% of patients with myelodysplasia undergoing reconstructive procedures (bladder augmentation and stoma placement) were obese, with 52% developing complications. (44) The authors found a significant association between complications and weight, with complications occurring in 40% of patients with normal weight and 40% of overweight patients versus 75% of obese patients. In addition, stomal stenoses and multiple complications were more prevalent in obese patients. As this translates to surgical risk, McDonald and colleagues evaluated body mass index (BMI) in a predominantly Hispanic population of children with spinal dysraphism and found that obesity rates and mean BMI increased with increasing age (ages 0–3 years, BMI 17.3 kg/m<sup>2</sup>; ages 4–10 years, BMI 18.4 kg/m<sup>2</sup>; ages 11–24 years, BMI 24.6 kg/m<sup>2</sup>). (45) Thus, it may behoove the pediatric urologist to operate on a patient at an earlier age to prevent obesity-associated surgical complications.



TABLE 1. Study Protocol for Urologic Care in Patients with Spina Bifida

	BIRTH-NICU	1–3 MONTHS	6–9 MONTHS	1–4 YEARS	5 YEARS
Evaluation	<ul style="list-style-type: none"> <li>• PVR</li> <li>• RBUS within 1 week or before discharge</li> </ul>	<ul style="list-style-type: none"> <li>• BP</li> <li>• DMSA scan</li> <li>• Serum creatinine</li> <li>• VUDS or VCUG (CMG + VCUG if no video capability)</li> <li>• RBUS</li> </ul>	6 months <ul style="list-style-type: none"> <li>• RBUS</li> <li>• If hostile bladder, repeat VUDS or VCUG/CMG 9 months</li> <li>• RBUS</li> </ul>	Annual <ul style="list-style-type: none"> <li>• Manual BP</li> <li>• RBUS</li> <li>• Serum creatinine 1–2 years</li> <li>• VUDS or CMG + VCUG (if +VUR on last study) 3–4 years</li> <li>• VUDS or CMG (+ VCUG if +VUR on last study)</li> </ul>	<ul style="list-style-type: none"> <li>• Manual BP</li> <li>• GFR/serum creatinine</li> <li>• RBUS</li> <li>• DMSA</li> <li>• VUDS or VCUG (only if +VUR on last study)</li> </ul>
Management	<ul style="list-style-type: none"> <li>• CIC every 6 hours vs indwelling catheter</li> <li>• Teach family CIC</li> <li>• Adjust CIC, maintain residuals &lt;30 mL</li> <li>• Stop CIC if &lt;30 mL at most checks for 3 days and grade 2 HN or lower</li> <li>• If &gt;grade 2 HN, continue CIC</li> </ul>	If hostile bladder <sup>a</sup> <ul style="list-style-type: none"> <li>• CIC q4h while awake</li> <li>• Oxybutynin 0.2 mg/kg TID</li> </ul> VUR Grades 1–4 <ul style="list-style-type: none"> <li>• If hostile bladder, CIC q4h while awake, oxybutynin 0.2 mg/kg TID + antibiotic prophylaxis</li> </ul> VUR grade 5: <ul style="list-style-type: none"> <li>• Begin CIC, oxybutynin 0.2 mg/kg TID + antibiotic prophylaxis</li> </ul>	Based on investigative findings	Based on investigative findings	Based on investigative findings

BP=blood pressure; CIC=clean intermittent catheterization; CMG=cystometrography; DMSA=dimercaptosuccinic acid; GFR=glomerular filtration rate; PVR=postvoid residual; q4h=every 4 hours; RBUS=renal and bladder ultrasonography; TID=3 times daily; VCUG=voiding cystourethrography; VUDS=video urodynamic study; VUR=vesicoureteral reflux.

<sup>a</sup>Hostile bladder refers to low compliant bladder, high bladder storage pressures, high detrusor leak point pressures, and severely trabeculated bladder. Data from Routh JC, Cheng EY, Austin JC, et al. Design and methodological considerations of the Centers for Disease Control and Prevention urologic and renal protocol for the newborn and young child with spina bifida. J Urol. 2016;196(6):1728–1734.

## Adolescence

Continued evaluation of renal function and bladder storage pressures is necessary through adolescence. A study followed patients with congenital spinal malformations from birth to a 12- to 18-year period to evaluate renal and functional outcomes. (46) Patients with no risk (no upper tract dilation, normal renal function and cystometry findings, and no significant postvoid residual) were followed annually with RBUS and cystometry. Patients classified as low- and high-risk were maintained on antibiotic prophylaxis, anticholinergics, and CIC, with biannual RBUS and cystometry as well as annual DMSA scans. These authors found that at adolescence, a majority (81%) performed CIC, 50% used anticholinergics, and 62% of patients were completely continent of urine. Overall, 19% of patients had undergone bladder augmentation, and none had developed end-stage renal disease; these rates are consistent with the existing literature. (28)(46)

Social continence becomes even more important in this age group and is reliant upon a successful bladder and bowel

regimen. CIC and anticholinergics remain the first-line therapy in addressing urinary incontinence. When refractory, intradetrusor botulinum toxin A injection is the next least invasive option. Although no high-level evidence exists supporting the efficacy of intradetrusor botulinum toxin A injections in this patient population, a systematic review of 12 published series showed that a majority reported resolution of incontinence in 32% to 100% of patients and improvements to varying degrees in decreasing maximum detrusor, increasing maximum cystometric capacity, and increasing bladder compliance. (47) By this age, if incontinence has not been satisfactorily treated, urinary reconstruction is often considered if it has not been performed already, usually around age 9 years. These complex procedures carry a high likelihood of morbidity, which is evident in an analysis of the Pediatric Health Information System database that found a 90-day readmission rate of 23% to 27%. (48) Careful patient selection, extensive preoperative counseling, and strong postoperative clinical support are

**TABLE 2. Summary of Management Options for Urinary Continence**

	<b>NONSURGICAL MANAGEMENT</b>	<b>SURGICAL MANAGEMENT</b>
Bladder storage/emptying concerns (low capacity, low compliance)	Clean intermittent catheterization Anticholinergics Overnight catheter drainage	Intravesical botulinum toxin Augmentation cystoplasty Urinary diversion
Low bladder outlet resistance		Injection of bulking agents into bladder neck Bladder neck sling Bladder neck reconstruction

Data from MacLellan DL, Bauer SB. *Neuromuscular dysfunction of the lower urinary tract in children*. Wein AJ, Kavoussi LR, Partin AW, Peters PA, eds. Campbell-Walsh Urology. 11th ed. Philadelphia, PA: Elsevier; 2016;chap 142: 3272–3296.

imperative for the success of reconstruction and to minimize postoperative complications.

In addition to maintaining bladder and renal-specific goals, clinicians should initiate counseling on sexual activity. (28) Both patient and clinician barriers exist in this area of patient care. For instance, for men with SB, few studies have assessed the quality and ability to have erections sufficient for intercourse. Roth and colleagues reported that 41% reported normal erections (from the validated Expanded Prostate Cancer Index Composite questionnaire), and patients with ambulatory status were more likely to report normal erections than nonambulators (63.1% vs 15.8%). VPS status did not seem to have a significant impact on erection status. (49) Sociosexual adjustment is a concern, because few adolescents with SB regularly date, and young adults express the need for sexual counseling. (17) Young patients with SB can feel intense worry about when and how to have discussions with their partners. (50) Adding complexity to the mix is the association of precocious puberty in girls with myelodysplasia, as found in 16% of girls in a series. (51) In such patients, the increased concentration of gonadal hormones leads to premature development of secondary sex characteristics and even psychosexual and behavioral changes.

From a clinician's perspective, broaching the topic may not come naturally. A study that explored the experiences of 10 pediatric urologists in providing sexual and reproductive health education to women with SB showed that they lack formal training, have knowledge gaps in sexuality, fertility, and pregnancy experience in the SB population, and have a lack of comfort and timing in having these conversations. Overall, the cohort of pediatric urologists did not feel prepared to provide sexual and reproductive health education for girls and women with SB despite this topic being within their scope of practice. (52) Though previous literature noted that patients would appreciate more guidance on how to discuss the impact of SB with their sexual partners, this

must be balanced with patient readiness and openness to the discussion. (28)

### Transitional Years

Now that over 80% of patients with SB survive into adulthood, transitional health care becomes increasingly important. For young adults with special needs, this is a dynamic, lifelong process with the goal of maximizing function and potential by providing uninterrupted, high-quality, developmentally appropriate health care services from adolescence to adulthood. (53) Physicians play a key role in this process because of the long-term and often close relationships cultivated with patients and their families, and young people are less likely to transition on their own. The American Academy of Pediatrics recommends creating a health-care transition plan with the patient and family by age 14 years. (53) Formulating an approach with these key stakeholders will motivate patients to become active participants in the transition process.

Transitioning patients with SB is complex and not always successful. In 1 center, only 40% of patients in a multidisciplinary SB clinic transitioned successfully to a transitional urology clinic or adult urologist, and those who did not transition were more likely to have emergency department visits. (54) Thus, it is important to identify barriers to transitional care and facilitating this transition for patients in the future. One of the most prominent barriers has been access to health-care clinicians who take care of adults with special needs. (55) Access to health care is multifaceted and heavily influenced by insurance status, physician coverage, and difficulty in navigating a complex health-care system. Grimsby et al discovered that more than one-quarter of patients who were referred to a transitional urology clinic missed their appointment, citing health insurance coverage issues as a reason in 47% of their cohort. (56) These findings influenced their practice to include dedicated social work and nursing visits to facilitate the transition process.

Providing a framework for the continuum of care is another major hurdle. No single approach will work equally well for all medically complex patients, nor can the health-care sector alone achieve success. What is known is that success depends on deliberate guidance. One such transition program has been established at the University of Oklahoma, which breaks the process of transitioning into stages based on age, maturity, and readiness as patients graduate from 1 level to the next. (10) Using this approach, the authors found that early and frequent meetings with the adult urologic team are critical for successful transitions to adult clinicians. Similarly, we have found that introduction of the patient to an adult urologist is essential to facilitate transition, and consistent attendance of this practitioner at our multidisciplinary clinic has been crucial.

### Adulthood

In addition to keeping the aforementioned goals in mind, adult patients with SB must face both ongoing and new challenges. While the transition of health care ought to be established earlier in life, studies have shown that a significant proportion of young adult patients either receive delayed care by adult physicians or lack regular health care altogether. (18)(54)(56) Unfortunately, rates of hospital admissions have been found to be over 12-fold higher in adults with SB than their age-matched counterparts. (57) In another study that similarly found high rates of hospital admission in this patient population, approximately one-third resulted from UTIs, highlighting the importance of prevention that could be addressed by regular outpatient follow-up visits.

Continence and reconstruction procedures discussed previously remain considerations into adulthood. In fact, in a retrospective study of 225 adult patients with SB, almost half had undergone some type of urologic procedure, and of those, 63% occurred after the age of 18 years. (58) In a cohort of 385 patients from a transitional clinic with a median age of 37 years and a median follow-up of 26 years, Husmann evaluated 3 outcomes implicated in increasing patient mortality after bladder augmentation: spontaneous bladder perforation, bladder neoplasia, and chronic renal failure. (59) Spontaneous rupture occurred in 3% with 1 associated death (0.25%). (59) Of the 203 patients followed for at least 10 years, 4% developed a bladder tumor, compared with 2.5% in an age-matched control population managed with anticholinergics and CIC; thus, it was concluded that augmentation is not significantly associated with an increased risk of cancer development. Chronic renal failure at stage 3 or higher occurred in 15%, and death occurred in 1% of the complete cohort. Interestingly, in the obese population, having a continent catheterizable channel conferred higher

compliance with CIC compared to patients having to catheterize, and those with continent channels were less likely to develop chronic renal failure ( $P < .001$ ). (59)

Regardless of reconstruction status, patients with SB have a higher incidence of stone disease, estimated to be 5% to 11% compared with 1% in the general population, which typically manifests in adulthood. (60) Moreover, patients with spinal deformity and neurogenic bladder who are surgically treated for stones have worse outcomes. Colangelo and colleagues found that, patients with spinal deformities had a lower stone-free rate than patients with normal anatomy (35.7% vs 61%) and a higher complication rate (40% vs 6.1%). (61) Christman and colleagues retrospectively reviewed a registry of patients undergoing ureteroscopy and found that bacteriuria was associated with stone episodes in 67% of patients with neurogenic bladders compared with 16.4% in controls; the median operative time was significantly longer in the neurogenic bladder cohort (80.5 vs 52 min); and stone clearance was lower at 63% in the neurogenic bladder cohort compared to 86.6% in controls. (62) In the SB population, endoscopic surgery for stones can be more challenging because of patient positioning issues as well as the need to navigate prior urologic reconstructions.

Finally, clinicians must continue to be aware of the possibility of bladder cancer in the SB population. Reports show that 70% of adults with SB undergo CIC and anywhere from 5% to 25% undergo augmentation cystoplasty. (58)(63) Rove and colleagues systematically reviewed patients with MMC who have bladder cancer and evaluated factors that could contribute to overall survival. They found that after removing patients who have bladder augmentation with a gastric segment, there was no difference in overall survival between patients with and without augmentation. However, those who did develop bladder cancer presented at a median age of 41 years (range 13–73 years), and 71% presented with stage III or IV bladder cancer with less than 50% overall survival at 1 year. (64) Higuchi and colleagues matched patients with bladder augments to a control group undergoing CIC; although there was no significant difference in the incidence of bladder cancer between the 2 groups (4.6% vs 2.6%), both groups had a higher risk of cancer than the general population. (63) Similar to Rove et al, the data of Higuchi et al also showed that bladder cancer occurs at a younger age in patients with neurogenic bladder managed with either CIC or bladder augmentation, and the disease is more advanced at the time of presentation.

### PARENTAL GUIDANCE

When a diagnosis of spinal dysraphism is made, families should be counseled extensively on the potentially life-altering

challenges their child may face. From a urologic standpoint, this includes frank discussions about bladder function, risk to renal function, and the need for lifelong surveillance and potential surgeries needed to preserve renal function and achieve urinary continence. When diagnosed prenatally, the MOMS trial should be discussed, including maternal and fetal risks and benefits as outlined herein so that an informed decision may be made about antenatal surgery. Explaining why an infant or child may need to perform intermittent catheterization in the context of preventing UTIs and renal damage and achieving acceptable urinary continence can help parental acceptance of the practice.

## SUMMARY

- Urologic care of patients with spinal dysraphism is lifelong and must be adapted to the unique challenges that patients face throughout the different stages of their lives.
- The initial evaluation should include, at a minimum, a postvoid residual measurement and RBUS; UDS, VCUG, and DMSA scans are also typically performed early to identify risk factors and evaluate renal function. (29)(30)(31)(32)(39)
- There is no clear consensus on the role of proactive bladder management with early CIC, though a study assessing a protocol of early CIC to optimize urologic care is ongoing. (39)
- Preserving renal function and achieving continence may require CIC, anticholinergics, intradetrusor botulinum toxin A injections, bladder neck bulking agents, or reconstruction with bladder augmentation and/or a bladder neck procedure.
- Transitioning care from pediatric to adult clinicians may prove to be one of the most challenging obstacles facing this complex patient population. Prominent barriers to accessing appropriate health care include limited number of professionals who treat adults with special needs and lack of insurance.
- In adulthood, bladder perforation, chronic renal disease, stone disease, psychosexual concerns, and bladder neoplasia are all issues treating clinicians must be aware of. (59)(60)(61)(62)(63)(64)

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Nongenetic etiologies for congenital defects / Environmental factors.
- Maternal metabolic disorders.
- Know the frequency of major congenital malformations.

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## NeoReviews Quiz

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1. Common causes of congenital lower urinary tract dysfunction include spinal dysraphisms such as myelomeningocele and sacral agenesis. Which of the following statements regarding spinal dysraphism is CORRECT?
  - A. The prevalence of spinal dysraphism is continuing to decline worldwide.
  - B. Spina bifida is more common in Asian newborns than in the general population.
  - C. The vast majority (95%-100%) of affected children currently survive to adulthood.
  - D. Sacral agenesis is defined as the absence of part or all of 2 or more sacral vertebral bodies.
  - E. Up to 50% of patients with sacral agenesis have a neurogenic bladder.
2. Myelomeningoceles are detected prenatally in 90% of cases. The Management of Myelomeningocele Study (MOMS) compared prenatal repair before 26 weeks of gestation to standard postnatal repair. Which of the following statements regarding the MOMS trial is FALSE?
  - A. Prenatal surgery resulted in a significant decrease in the need for a cerebrospinal fluid shunt by age 12 months.
  - B. Children who underwent prenatal surgery had improved independent ambulation at age 30 months.
  - C. The risk of preterm birth was 79% in the prenatal repair group compared with 15% in the postnatal repair group.
  - D. Prenatal surgery is associated with significantly less vesicoureteral reflux.
  - E. Prenatal surgery significantly decreased the need for clean intermittent catheterization (CIC) at age 30 months.
3. One of the primary goals in management of the neurogenic bladder is to prevent renal damage by ensuring safe bladder storage pressures and adequate bladder emptying at low pressures. Which of the following statements regarding assessment and early management strategies for neurogenic bladder is FALSE?
  - A. The level of the spinal injury can be used to predict the degree or type of lower urinary tract dysfunction.
  - B. Renal and bladder ultrasonography, voiding cystourethrography (VCUG), functional imaging, and urodynamic studies are recommended for all patients with spinal dysraphism, including those with sacral agenesis.
  - C. Proactive management with initiation of CIC in the newborn period prevents renal deterioration and is recommended for all patients with spinal dysraphism.
  - D. The presence of external sphincter dyssynergia is a risk factor for future renal function deterioration.
  - E. Urodynamic studies are helpful to determine the presence of bladder capacity and compliance changes in patients with spina bifida.
4. Patients with spinal dysraphism are at increased risk of developing urinary incontinence, defined as involuntary leakage of urine. Which of the following statements regarding urinary continence in adolescents is CORRECT?
  - A. About 50% of adolescent patients perform CIC to maintain continence.
  - B. Most (80%) adolescent patients use anticholinergics to help improve continence.
  - C. In refractory cases, intradetrusor botulinum toxin A injection results in the resolution of incontinence in up to 100% of cases.
  - D. Fewer than 10% of adolescents have undergone bladder augmentation surgery.
  - E. Overall, 40% of adolescent patients are completely continent of urine.

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5. Patients with neurogenic bladder secondary to spinal dysraphism have continued medical need requiring a coordinated approach to transition of care to adult providers. Which of the following statements regarding long-term outcomes of patients with spina bifida is CORRECT?
- A. Adults with spina bifida have a 6-fold increased rate of hospital admission compared with age-matched adults.
  - B. Adults with spina bifida have a 5% to 11% incidence of stone disease compared with less than 1% in the general population.
  - C. Bladder reconstruction is rarely performed in adulthood, with most surgeries occurring before age 18 years.
  - D. Chronic renal failure occurs in 30% of adults with spina bifida.
  - E. Although patients with spina bifida have a higher incidence of bladder cancer, they typically present with early-stage disease.

# The Effect of Preterm Birth on Renal Development and Renal Health Outcome

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## Education Gaps

1. Clinicians should be aware that preterm birth is associated with a reduced functional nephron mass, predisposing an individual to chronic kidney disease and quicker progression to end-stage chronic kidney disease.
2. Patients and health-care professionals must take an active role in protecting the kidneys of preterm survivors from further injury throughout life.

## Abstract

Preterm birth is associated with adverse renal health outcomes including hypertension, chronic kidney disease, and an increased rate of progression to end-stage renal failure. This review explores the antenatal, perinatal, and postnatal factors that affect the functional nephron mass of an individual and contribute to long-term kidney outcome. Health-care professionals have opportunities to increase their awareness of the risks to kidney health in this population. Optimizing maternal health around the time of conception and during pregnancy, providing kidney-focused supportive care in the NICU during postnatal nephrogenesis, and avoiding accelerating nephron loss throughout life may all contribute to improved long-term outcomes. There is a need for ongoing research into the long-term kidney outcomes of preterm survivors in mid-to-late adulthood as well as a need for further research into interventions that may improve ex utero nephrogenesis.

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### ABBREVIATIONS

AKI	acute kidney injury
CKD	chronic kidney disease
CysC	cystatin C
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
FGR	fetal growth restriction
GA	gestational age
GFR	glomerular filtration rate
LBW	low birthweight
SBP	systolic blood pressure

## Objectives After completing this article, readers should be able to:

1. Improve awareness of NICU professionals on how to protect kidneys of preterm infants from further injury, particularly during the period of ex utero nephrogenesis.
2. Encourage surveillance of preterm survivors in childhood and adulthood to reduce obesity and observe for evidence of hypertension or insulin resistance to minimize further "hits" to an already reduced nephron mass.

3. Stimulate research in areas where there are gaps in the evidence, in particular long-term follow-up of cohorts of preterm survivors into late adulthood.

## INTRODUCTION

Fifteen million births occur before 37 weeks' gestational age (GA) worldwide each year. (1) Over the past decade, preterm birth rates in the United States have varied between 9.8% and 11.4% and currently are at 9.9%. (2)(3) Around 2.8% of births are early preterm births occurring before 34 weeks' gestation. (2) Although this group experiences a greater proportion of long-term morbidity, all preterm infants have higher rates of morbidity than their term-born contemporaries. (3) The preterm population is diverse in both GA and the underlying cause for prematurity. Conditions associated with an adverse intrauterine environment include preeclampsia, multiple births, and chorioamnionitis, and account for 38% of preterm deliveries. (3)

The renal consequences of preterm birth are becoming increasingly recognized and include a higher risk of chronic kidney disease (CKD), (4) a quicker progression of renal pathology, (5) and a predisposition toward hypertension. (6) CKD is associated with significant morbidity and mortality and is estimated to affect 14% of the US population. (7) The global burden of disease study highlighted that CKD is a growing public health problem that is increasingly contributing to global mortality. (8) As the preterm population surviving into childhood and adulthood grows, there is an increasing need to better understand the renal long-term effects of preterm birth and to identify ways to reduce morbidity associated with preterm survival.

## NORMAL RENAL DEVELOPMENT

Renal development begins with the differentiation of the pronephros in the third week of gestation followed by the mesonephros at 4 weeks of gestation. (9) The pronephros is nonfunctional in humans and involutes whereas the mesonephros transiently functions as an excretory structure until the definitive kidney develops from the metanephros. (10) The metanephros gives rise to the ureteric bud which undergoes branching; through reciprocal signaling, the branching of the ureteric bud progresses, and the mesenchyme differentiates to form the renal vesicles. The renal vesicles ultimately form the glomeruli, tubules, and loop of Henle of the mature nephron, with the first glomeruli present from 9 to 10 weeks' gestation and fetal urine

production beginning at 10 weeks. (9) The fetus becomes the main producer of amniotic fluid from around 16 weeks' gestation. (9) Maximal human kidney growth has been shown to occur toward the end of the second and beginning of the third trimester between 26 and 34 weeks' GA, (11) with nephrogenesis complete by term GA. (12)

Perinatal autopsy studies have demonstrated that there is individual variation in the GA at which nephrogenesis is complete; 1 group examined normally grown fetuses, demonstrating ongoing nephrogenesis at 31 weeks' GA and complete nephrogenesis in all infants by 38 weeks' GA, with some variability in those between 35 and 37 weeks. (12) Another group demonstrated that nephrogenesis was complete by 32 weeks' GA in some fetuses. (13) Term infants are born with the total number of nephrons that they will have in their lifetime; optimizing nephrogenesis is advantageous for the long-term renal health of an individual.

## NEPHROGENESIS IN THE PRETERM INFANT

Many preterm infants are born at a time when they are still undergoing nephrogenesis, with some born before reaching their maximal period of nephron development. Nephron development continues after very preterm birth with active glomerulogenesis, characterized by the presence of basophilic S-shaped bodies, and continuing until 40 days' postnatal age. (14) Extremely preterm infants more than 40 days old who experienced acute renal failure (defined as a sustained elevation in creatinine  $>2.0$  mg/dL) have fewer nephrons than preterm infants without a history of renal failure. During normal kidney development, nephrons grow from the corticomedullary junction toward a nephrogenic zone situated below the renal capsule, forming nephron "generations." (13) The newest nephrons are therefore situated in the outer renal cortex. An autopsy study has recently shown that many preterm infants have abnormal glomeruli in their outer renal cortex, implying that nephrons that develop ex utero may not develop normally. (13) Autopsy studies have also shown that preterm birth is associated with accelerated renal maturation and the presence of a larger proportion of morphologically abnormal glomeruli compared with gestation-matched stillborn controls. (13) It is clear that the number of nephrons that form in

the first 4 to 6 weeks after delivery is important in establishing the lifelong nephron mass of a preterm infant and that this should be supported as much as possible by avoiding postnatal kidney injury.

Preterm birth and reports of its effect on the glomerular filtration rate (GFR) have been contradictory. Preterm infants born before 32 weeks' GA were found to have a reduced estimated GFR (eGFR), measured using cystatin C (CysC) at term postmenstrual age. (15) In contrast, an extremely preterm cohort of less than 28 weeks' gestation at birth was shown to have an eGFR comparable to that of term infants using urinary CysC despite having smaller kidneys, leading the authors to conclude that this may be evidence of glomerular hyperfiltration and compensation for reduced nephron mass. (15)

## NEPHRON MASS

Nephrons are the functional units of the kidney; the nephron mass of an individual refers to the total number of functioning nephrons a person has at any given time. (16) Data regarding normal human nephron number and density have predominantly been determined histologically from autopsy studies or from renal transplant donors. There is large variation in nephron number and density between individuals with 4- to 8-fold variations in nephron number observed at autopsy. (10) The reason for this degree of variability between individuals is not fully understood but is likely related to an interplay among genetics, the environment of an individual during nephrogenesis, and renal insults that occur over the course of a lifetime. (12)(17) Nephron mass naturally declines with age; a study examining the kidneys of healthy renal transplant donors demonstrated a 48% difference in the nonsclerotic glomerular number between donors aged 19 to 28 years and those aged 70 to 75 years. (18) Older donors have more sclerotic glomeruli. (18)

A reduced nephron mass has been associated with CKD (19)(20) and hypertension (21) in adulthood. Because it is not possible to directly measure nephron mass in living subjects, kidney size, and in particular, kidney length and volume, are often used as surrogate markers of nephron mass. (22) Unfortunately, ultrasonography has been shown to underestimate true renal volume by a median of 24% (range 5%–48%) in an animal model. (23) It has been proposed that measuring the renal parenchyma using ultrasonography may be a more reproducible and potentially more accurate tool for estimating normal and abnormal renal development. (24) Normal kidney size and volume do not differentiate between normal growth and compensatory hypertrophy of an oligonephronic kidney. (25) Renal

parenchymal thickness has been shown to be closely associated with renal volume, (26) and renal cortical thickness has been shown to be correlated with renal function in adults. (27) Currently, renal volume as seen on ultrasonography cannot be considered a surrogate for nephron number.

Examining the effects of nephron mass on renal function is challenging; noninvasive estimates of GFR vary in accuracy. The gold standard plasma and urinary clearance studies are accurate but invasive, whereas other noninvasive estimates of GFR have been shown to be accurate at predicting a population mean but not individual GFR, (28) limiting their clinical usefulness at the bedside. Noninvasive calculated eGFR values are often used in clinical studies, because they are more acceptable to study participants. A number of alternative biomarkers to creatinine have been used to measure GFR, in particular CysC (29); however, again, the accuracy of this biomarker to estimate GFR is variable. The development of new real-time measured GFR using transdermal sensors that detect fluorescent filtration markers may change the way in which both clinicians and researchers are able to measure and study the effect of nephron mass on renal function, as well as the impact on both acute kidney disease and CKD. (30)

## DEVELOPMENTAL PROGRAMMING AND NEPHROGENESIS

David Barker first observed that in utero events are associated with adult disease and described the “Barker hypothesis,” which underpins current theories around the developmental origins of health and disease. (31) Brenner et al hypothesized that this principle could be applied to kidney development, postulating that reduced nephron numbers could predispose a person to hypertension. (32) Glomerular hypertrophy is thought to occur in response to reduced nephron mass and glomerular hypertension (maintaining glomerular surface area), leading to hyperfiltration, salt sensitivity, sodium and water retention, hypertension, and glomerulosclerosis.

### Support for the Brenner Hypothesis

It has been demonstrated that glomerular surface area is similar between individuals with different kidney sizes, supporting the theory that glomerular hypertrophy occurs in oligonephronic kidneys. (33) Glomerular hypertrophy has been shown to be more prevalent in populations with a higher risk of CKD, including Australian aboriginal and black populations. (5) Glomerular hypertrophy has also been associated with poor post-transplantation outcomes. (5) Autopsy studies have shown a large variability in nephrogenesis in

fetal life, thus supporting the hypothesis that the intrauterine environment influences kidney development. (12)

### Low Birthweight

Birthweight has been demonstrated to be an important predictor of nephron and glomerular mass. (12)(21)(34)(35) Low birthweight (LBW <2.5 kg) has been associated with the development of end-stage renal failure, (36)(37) CKD, (19)(38)(39) and a more rapid deterioration in renal function in patients with underlying kidney disease. (5) Some infants are LBW as a result of prematurity, others are term but have experienced fetal growth restriction (FGR), and some are both growth restricted and preterm. Preterm birth is estimated to account for up to 80% of the LBW population. (40) FGR has various causes, including placental insufficiency and maternal smoking, which are often associated with an adverse intrauterine environment for a developing fetus. (41) The hypotheses underlying why LBW is associated with CKD vary depending on the etiology. In normally grown preterm infants, it is likely a result of an interruption in normal organ and vascular growth followed by ex utero nephrogenesis altered by the postnatal environment. In term infants born after a pregnancy complicated by placental insufficiency, the fetal kidneys may not have received adequate nutrition or oxygenation for nephron development. (42)(43) Many preterm infants are subjected to both the effects of being born during nephrogenesis and by an adverse intrauterine environment for organ development.

### Maternal Diet and Nutrition

Maternal diet and nutrition during pregnancy have been shown to influence fetal nephrogenesis. (44) Micronutrient deficiencies, including vitamin A, iron, and folate, may affect human renal growth while macronutrient deficiency, in particular protein deficiency, has been shown to affect fetal renal growth in animal studies. (44)

### Antenatal Drugs

Smoking is a risk factor for preterm birth. Cigarette exposure in pregnancy has a demonstrated dose effect, with the more cigarettes smoked per day increasing the risk of preterm birth. (45) Nicotine causes vasoconstriction and reduces placental blood flow. Maternal smoking during pregnancy has been associated with a smaller kidney volume and lower eGFR in school-age children (46) and a smaller kidney size in both fetuses and newborns. (47) A large retrospective cohort study in Japan found that maternal smoking was an independent risk factor for proteinuria at age 3 years in offspring. (48) In animal studies, ethanol use has been shown to reduce nephron number in

offspring. (49) An Australian cohort study has demonstrated an association between maternal alcohol use in pregnancy and mild CKD in offspring during their 30s. (50)

Many preterm infants are exposed to in utero medications aimed at improving their survival and outcomes, a number of which may have an impact on nephrogenesis. Atosiban, which is an oxytocin receptor antagonist sometimes used as a tocolytic to delay preterm labor, may reduce renal cell growth, renal vasodilation, and the carbonic anhydrase activity. (51) Corticosteroids have been shown to reduce nephrogenesis in animal models and upregulate the expression of angiotensin II and its receptors. (51) Antibiotics (in particular aminoglycosides) and nonsteroidal anti-inflammatory drugs also cross the placenta and may affect fetal renal function. (52) Indomethacin is known to reduce amniotic fluid volume as a result of fetal renal dysfunction. Indomethacin in a neonatal rat model has been shown to cause glomerular injury and reduce glomerular number in adulthood, suggesting that indomethacin should be avoided if other less nephrotoxic medications are available. (53)

## THE POSTNATAL ENVIRONMENT AND NEPHROGENESIS

Significant physiologic changes occur after preterm birth, which lead to structural and functional changes in the developing kidney. The renal perfusion pressure of a fetal kidney is estimated to be around 3% of the cardiac output, which increases to 15% after delivery. (54) A sudden change in glomerular vascular resistance has been proposed as a possible mechanism for glomerular injury after preterm birth. (55)

### Hyperoxia

Nephrogenesis and ureteric branching ordinarily occur in a hypoxic environment, with animal studies showing that mice undergoing nephrogenesis in a physiologically hypoxic environment had more ureteric branches and larger kidneys than those in a physiologically hyperoxic environment. (43) Conflicting results demonstrating worsened ureteric branching and smaller kidneys in a hypoxic environment have been seen in a similar mouse model, raising questions about whether kidneys respond to hyperoxia differently during different stages of nephrogenesis. (43) Another mouse model examining the effects of hyperoxia after preterm birth demonstrated a reduced glomerular count in pups with retinopathy of prematurity exposed to a hyperoxic environment, (56) again suggesting that hyperoxia impairs nephrogenesis. The arterial oxygen tension increases suddenly after preterm birth, altering the environment in which organogenesis occurs. Hyperoxia and



hypoxia have both been shown to be deleterious to the outcomes of preterm infants and both should be avoided in the NICU whenever possible. (57)

### Nephrotoxin Exposure

Nephrotoxic medications are widely used in NICUs worldwide, (58)(59)(60) with the smallest and least mature infants often experiencing the largest exposures. In a retrospective review of infants born weighing less than 1,500 g, it was demonstrated that the majority of nephrotoxin exposure occurred in the first 40 days of age, which coincides with the period of ex utero nephrogenesis. (60) It has been shown that up to 87% of very-low-birthweight infants in NICUs are exposed to more than 1 nephrotoxic medication, most commonly gentamicin, indomethacin, or vancomycin, up to a total of 2 weeks in their hospital stay. (59)

Aminoglycoside antibiotics are widely used in the NICU, often as empiric therapy for suspected early- or late-onset infection. Aminoglycosides can accumulate in the kidney, leading to high concentrations in the renal cortex and ultimately leading to tubular injury. (61) Aminoglycoside-associated acute kidney injury (AKI) is generally felt to be less prevalent in newborns than in older children or adults; however, it can still lead to significant tubular damage and injury. (62) Nonsteroidal anti-inflammatory medications are often used in preterm infants to treat a patent ductus arteriosus, and indomethacin may be used as prophylaxis for intraventricular hemorrhage. Both act as prostaglandin inhibitors, which lead to vasoconstriction and reduced blood flow in renal and mesenteric vessels in addition to the intended vasoconstriction of the patent ductus arteriosus. (63) Animal studies have demonstrated that both ibuprofen and indomethacin reduce cyclooxygenase 2 and vasodilator prostanoids, with indomethacin having a more profound effect than ibuprofen. (64) This reduces renal blood flow and often leads to oliguria. Ibuprofen use in preterm infants has been shown to reduce GFR in the first month of age, (65) whereas indomethacin use has been shown to increase urinary podocyte and albumin concentration in the urine of preterm infants of less than 33 weeks' GA compared with preterm and term controls, suggesting that it causes glomerular injury. (66) Although ibuprofen was found to cause glomerular injury in a neonatal rats, it did not result in reduced glomerular number in adulthood. (67)

A recent retrospective review of newborns weighing less than 1,500 g and of less than 30 weeks' gestation found that the prevalence of AKI increased with decreasing GA, decreasing birthweight, and increasing nephrotoxic medication exposure. (60) Given that nephrotoxin administration is a potentially controllable risk factor for AKI, this has

become the focus of a clinical practice improvement project: the Nephrotoxin Injury Negated by Just-in-time Action (NINJA). Implementing an initiative that triggers daily creatinine measures in noncritically ill children who are either receiving 3 simultaneous nephrotoxins or have received an aminoglycoside for more than 3 days has been shown to reduce AKI by 68%. (68) Trials of this approach need to be conducted in neonatal populations.

### Acute Kidney Injury

Preterm infants have a high incidence of AKI; extremely preterm infants of less than 29 weeks' GA have been shown to have an incidence of 47.9% using the modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria. (69) The preterm population of 29 to 36 weeks' GA, in whom adverse long-term outcomes have been traditionally less concerning, has an incidence of AKI of 18.3%. (69) Although AKI has been independently associated with mortality in a preterm population (<1,200 g or <31 weeks' gestation), (70) as previously mentioned, it is also associated with reduced nephron mass. (14)

Although some epidemiologic evidence exists to support an association between AKI and CKD in pediatric populations, (71)(72), more work needs to be done to show a causal link between pediatric or neonatal AKI and adult CKD. The IRENEO prospective cohort study has shown a reduced kidney volume but no difference in eGFR at a median age of 6.6 years in former preterm newborns (<33 weeks' GA) who survived neonatal AKI compared with control subjects. (73) Although the investigators demonstrated no difference in eGFR between groups, the overall population had a high incidence of albuminuria and diminished eGFR. Similarly, the Follow-up of AKI in Neonates during Childhood Years (FANCY) study showed that extremely low-birthweight newborns who experienced AKI in the NICU had a more than 4-fold increased risk of renal dysfunction at a median age of 5 years compared with control subjects (74) and again demonstrated a high incidence of low eGFR of less than 90 mL/min per 1.73 m<sup>2</sup> (26%) in their entire cohort. When possible, efforts should be made to prevent AKI in preterm populations.

### Postnatal Nutrition

The evidence to guide clinicians about what constitutes optimal postnatal nutrition for ex utero nephrogenesis is limited. Animal models have shown that increasing growth through overfeeding postnatally may lead to an increase in nephron mass without any improvement in the risk for hypertension or renal dysfunction. (75) A rat model demonstrated that early postnatal overnutrition led to an

increase in weight gain and 20% increase in nephron number in overfed offspring compared with normally fed offspring. (75) Despite their increased nephron number, overfed male rats were more likely to have hypertension, proteinuria, and glomerulosclerosis relative to controls. Neonatal high-protein diets have been shown to be associated with glomerular hypertrophy and glomerulosclerosis in an FGR rat model, (76) but to a lesser extent in an FGR piglet model. (77)

A single-center prospective cohort study demonstrated that postnatal growth failure is associated with a reduced GFR relative to controls in a human preterm population. (78) Ensuring optimal nutrition in this population is challenging because human evidence supports the idea that catch-up growth leading to obesity in preterm infants may worsen the progression of proteinuric kidney disease and that obesity and prematurity are additive factors. (79) A cohort study examining 153 former preterm infants at a median age of 11.5 years demonstrated that rapid weight gain in early childhood (>1 year of age) was associated with a higher body fat percentage and worsened metabolic markers of insulin resistance and hypertension relative to controls whereas rapid weight gain in infancy (<1 year of age) was not. (80)

## LONG-TERM RENAL EFFECTS OF PRETERM BIRTH

Growing evidence demonstrates that prematurity has an impact on long-term renal health (Table). As large cohorts of preterm survivors continue to reach adulthood, more information is being gained about their long-term medical outcomes. Although a number of preterm cohorts have been followed up into early adulthood, we are yet to fully understand the effects of preterm birth on morbidity in mid-to-late adulthood.

### Nephrocalcinosis

Preterm infants are at an increased risk for calcium deposition in the kidney, known as “nephrocalcinosis.” This has a variable incidence in the literature and is thought to be associated with decreasing birthweight (81)(82); increased calcium, phosphorus, and ascorbic acid intake; and increased exposure to furosemide, dexamethasone, thiazides, and theophylline. (81) A matched cohort study in Greece examined 105 infants born before 36 weeks’ GA and found evidence of mild tubular dysfunction and a reduced kidney length in those with nephrocalcinosis relative to controls at 1 year of age. (83) Kist-van Holthe et al also demonstrated that former preterm children born at less than 32 weeks’ GA with nephrocalcinosis were more likely to have mild renal insufficiency

and tubular dysfunction compared with control subjects at a mean age of 7.5 years. (84) These findings suggest that preterm infants with nephrocalcinosis may be at an increased risk of developing long-term renal dysfunction into adulthood; however, this has not yet been demonstrated in the literature.

### Kidney Size, Growth, and Function

As previously discussed, kidney size and volume are used as noninvasive markers of nephron mass. Preterm infants have smaller kidneys at term postmenstrual age than their term-born contemporaries; however, preterm infants have been shown to have larger kidney-to-bodyweight ratios, (13)(14)(15) potentially because of glomerular hypertrophy. A population of preterm infants has recently been shown to exhibit catch-up renal growth over the first 6 months of age. (85) Preterm infants born at 30 to 32 weeks’ GA were shown to have smaller kidneys at term postmenstrual age than term-born controls; however, they subsequently exhibited an increased renal growth rate, leading to similar kidney length at 6 months’ corrected age. (85) Their renal cortical regions grew more during this period of catch-up growth while their medullary regions remained smaller. The cause for this catch-up growth is uncertain; however, this suggests that while catch-up growth may occur, this is not necessarily associated with normal renal development.

A number of groups have examined former preterm infants’ kidney sizes in adulthood. The renal volumes of 20-year-old former premature female survivors (small for GA and appropriate for GA) have been shown to be smaller (both length and volume) compared with term controls. This association was seen irrespective of whether the study participants were small or appropriate for GA at birth. (86) More recently, the Health of Adults Born Preterm (HAPI) cohort study performed in Canada showed that adults born at less than 29 weeks’ GA had smaller kidneys as young adults (average age 23 years) compared with matched term-born controls. (6) Their renal volume corrected to body surface area was 10% lower than controls. There was no difference in eGFR between groups; however, young adults born preterm had higher albumin-to-creatinine ratios (albeit still within the normal range) relative to term-born controls, suggesting that they may have reduced glomerular endothelial integrity. (6)

Prematurity has been demonstrated to have an impact on kidney function. At 11 years of age, former preterm infants have been shown to have a reduced eGFR measured by urinary CysC and symmetric dimethylarginine compared with term controls. (87) A Polish cohort study has shown that in children born extremely preterm, eGFR measured

using CysC was significantly higher in former preterm infants at both 7 and 11 years of age compared with matched term controls. Their eGFR worsened slightly over time, implying that long-term follow-up would be prudent. (88) Not all longitudinal studies have shown a reduction in eGFR during mid-childhood. Vieux et al's cohort in France (27–31 weeks' gestation evaluated at 5 years of age) all had normal eGFRs in follow-up. (89) As many former preterm cohorts continue to age, it is important to monitor their renal function longitudinally to gain a better understanding of

how these early changes in kidney function and structure manifest themselves in mid-to-late adulthood.

### Chronic Kidney Disease

A recent large Swedish cohort study demonstrated that extremely preterm infants (<28 weeks' GA) have a 3-fold risk of developing CKD (odds ratio 3.01 [1.67–5.45]) and that late preterm infants have a risk that is almost twice that of term infants (odds ratio 1.84 [1.62–2.08]). (4) This association was strongest in childhood and persisted until

TABLE. **Summary of the Effects of Preterm Birth on Renal Health Outcome**

RISK FACTOR			RENAL HEALTH OUTCOME
Antenatal period	Maternal malnutrition		Poor renal growth (44)
	Maternal smoking		Increased risk of preterm birth (45) Smaller kidney volume and eGFR at school age (46)(47) Proteinuria at 3 years of age (48)
	Maternal alcohol consumption		Mild CKD in offspring in their 30s (39)
Perinatal period	Low birthweight		Increased risk of end-stage renal failure (36)(37) Increased risk of chronic kidney disease (19)(38)(39) More rapid decline in kidney function when there is underlying kidney disease (21)
	Ex utero nephrogenesis		Abnormal glomerulogenesis (26)(40)
	Acute kidney injury		Reduced nephron mass (14) Mortality (70)
	Postnatal growth failure in very-low-birthweight infants		Reduced GFR relative to term controls (78)
Childhood and adulthood	Preterm birth	Renal size and function	Smaller kidney size relative to term born controls (6)(86) Larger kidney to bodyweight ratio relative to term born controls (13)(14)(15)
		Renal function	Increased risk of nephrocalcinosis (81)(82) Higher albumin to creatinine ratios than term born controls in young adulthood (6) Reduced eGFR relative to term born controls at 7–11 years of age (87)(88) Increased risk of chronic kidney disease persisting into mid-adulthood (4)
	Hypertension		Alterations in the function of the renin-angiotensin system (6)(90)(91) Higher blood pressure than term controls in childhood and adulthood (92)(93)(94)(95) A greater hypertensive effect in former preterm women than men (95)(96) Increased salt sensitivity (ie, blood pressure changes in relation to a high salt diet) (97)
	Nutrition		Obesity is an additive risk factor to prematurity for proteinuric kidney disease (79) Greater risk of insulin resistance (99)

eGFR=estimated glomerular filtration rate; CKD=chronic kidney disease.

midadulthood in all groups. There was a strong inverse association between GA and CKD, which included children born at what is typically considered full term at 37 and 38 weeks' GA. This study relied on medical coding data to make a diagnosis of CKD, which means that the investigators could have under- or overestimated the true incidence of CKD in this population. Importantly, 24% of those who experienced acute renal failure in the neonatal period (27% of whom were preterm) were subsequently diagnosed with CKD.

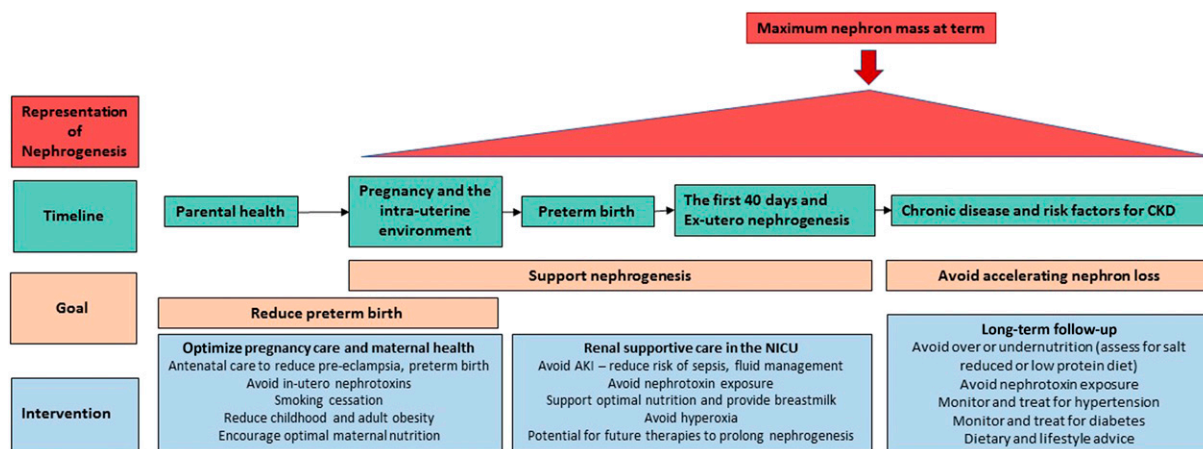
## Hypertension

Preterm birth is associated with an increased risk of hypertension. The underlying etiology of this association is not fully understood and is likely to be multifactorial. Prematurity and exposure to antenatal steroids have been associated with alterations in the function of the renin-angiotensin system. (90) A recent cohort study showed that angiotensin I levels are elevated in preterm infants relative to term infants and that changes in blood pressure in preterm infants occurred in association with changes in renin and angiotensin peptides, (6) which were not seen in term controls. Alamandine, a vasodilatory counterregulatory peptide moderated by the renin-angiotensin system, (91) has also been shown to be elevated in hypertensive preterm survivors but not in hypertensive term-born participants. It has been theorized that this represents a counterregulatory cardiovascular and renoprotective activation in preterm survivors.

A meta-analysis of observational studies found that preterm birth is associated with a 2.2 mm Hg increase in systolic blood pressure (SBP) compared with term controls. (92) These studies were from different countries and reported outcomes at varied ages until early adulthood.

The incidence of hypertension was also increased in those born preterm. The reason for this association is not fully understood. Studies published since this systematic review have continued to demonstrate increases in both SBP and diastolic blood pressure (DBP) in those born preterm. Edstedt Bonamy et al showed that both SBP and DBP were higher (although not abnormal) in children born preterm compared with control subjects at 6 years of age. (93) An individual patient meta-analysis including 9 international cohort studies recently demonstrated a 3.4 mm Hg increase in SBP and a 2.1 mm Hg increase in DBP in adulthood in those born with very low birthweight compared with control subjects, (94) with a larger hypertensive effect noted in former preterm women than men and in those infants whose mothers had preeclampsia. A cross-sectional study of 5,232 young adult women in Sweden (mean age, 18 years) showed that those born preterm had an elevated SBP and mean blood pressure relative to those born at term. (95) A meta-analysis performed by Parkinson et al also showed an association between increased SBP and DBP affecting women more than men. (96) Some observational evidence shows that some preterm infants may exhibit salt sensitivity (ie, changes in blood pressure with a higher salt diet). (97)

Hypertension causes glomerulosclerosis and is a risk factor for CKD and progression to end-stage CKD. (98) In a population that begins life with fewer nephrons, ensuring that hypertension is both detected and treated appropriately is important. Evidence shows that preterm infants, particularly those born small for GA, are at an increased risk for insulin resistance and metabolic syndrome. (99) Diabetes is also strongly associated with end-stage CKD, (98) making it important to identify those with insulin resistance early to avoid nephron loss.



**Figure.** Timeline of nephrogenesis outlining potential opportunities to support renal development in preterm infants. AKI=acute kidney injury; CKD=chronic kidney disease.

## INTERVENTIONS AIMED AT IMPROVING NEPHROGENESIS AND LONG-TERM RENAL HEALTH OF PRETERM SURVIVORS

Interventions aimed at improving the long-term renal health of preterm infants need to be multipronged (Figure). The starting point of any preterm infant's increased risk of mortality and morbidity is the point at which they are born early; any intervention aimed at reducing the risk of preterm birth is therefore of huge potential benefit. A large proportion of preterm birth remains unexplained; however, there are interventions that have reduced the incidence of preterm birth in specific high-risk groups, the details of which are beyond the scope of this review. (100) Given that many preterm infants experience the "double hit" of both preterm birth and growth restriction, interventions that reduce risk factors for FGR are also of benefit; this includes smoking cessation, advice during (and ideally before) pregnancy with regard to smoking, drug use, and good maternal nutrition both around the time of conception and throughout pregnancy. The first 1,000 days is an international public health initiative aimed at optimizing the nutrition of infants from conception to their second birthday to reduce their risk of programmed noncommunicable diseases. (101) Other obstetric interventions such as screening for the risk of preterm preeclampsia and providing aspirin to those who qualify could potentially reduce iatrogenic preterm birth. (102)

Once preterm birth has occurred, attention should be given to reducing renal injury during ex utero nephrogenesis. This includes reducing the risk of sepsis in the NICU, which is associated with AKI, avoiding hyperoxia, and reducing exposure to nephrotoxins. The evidence around what constitutes optimal nutrition for nephrogenesis is limited; however, human milk feeding (either expressed maternal milk or banked breast milk) has been associated with a reduction in hypertension in adolescents born preterm in nonrandomized studies. (103)

Ideas for novel drug and stem cell therapies aimed at prolonging nephrogenesis in preterm infants are being discussed and explored in the literature (104)(105)(106); however, at this stage (to our knowledge) these have not progressed to preclinical trials.

Given the increased risk that preterm survivors have for hypertension and decreased insulin sensitivity, this population should be followed throughout childhood and adulthood to ensure that they receive appropriate diagnosis and treatment. Health-care professionals and people born preterm should receive education and advice regarding their increased risk for CKD and the importance of lifestyle interventions.

## FUTURE DIRECTIONS

Many gaps remain in our understanding of the effects of preterm birth on long-term renal health. As preterm cohorts are followed up into mid-to-late adulthood, we will gain further knowledge of their risk profiles and renal complications, which will continue to help guide future research, intervention, and therapies. As new technology such as real-time measured transcutaneous GFR becomes available, we may be able to better identify and target our highest risk populations and ensure that they receive appropriate follow-up.

## CONCLUSIONS

Preterm birth leads to a reduced functional nephron mass and to maladaptation of the kidney. This in turn predisposes preterm survivors to reaching the threshold of glomerulosclerosis at which renal function declines earlier in life. There is still a lot to learn about the effects of prematurity on the kidney and how to best support the kidneys of preterm survivors, which should remain a focus for ongoing research. Currently many opportunities exist for clinicians to avoid further contributing to nephron loss in preterm infants. These include avoiding neonatal AKI and nephrotoxin exposure during nephrogenesis; educating preterm survivors and their families about lifestyle risks that may contribute to nephron loss; and educating primary health care professionals about the importance of reducing obesity, screening for hypertension and insulin resistance, and avoiding nephrotoxins in former preterm children and adults.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations, imaging, and laboratory features of renal failure in the neonate.
- Hypertension.
- Know how prenatal diagnosis of renal abnormalities affects postnatal management.
- Know the recommended supportive and corrective treatment of anatomic abnormalities of the kidneys and urinary tract in infants.
- Recognize the clinical manifestations of anatomic abnormalities of the kidneys and urinary tract in infants.
- Know the effects of drugs such as cyclo-oxygenase inhibitors, angiotensin-converting enzyme inhibitors, prostaglandins, and catecholamines on renal function (antenatal and postnatal).
- Know the changes in glomerular and tubular function that occur during development, including the handling of glucose, sodium, potassium, calcium, bicarbonate, and phosphate.



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# Index of Suspicion in the Nursery

## 1 Lethal Pulmonary Hemorrhage in a 3-day-old Term Infant

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### PRESENTATION

A 38-1/7-week-gestation girl is born to a 21-year-old gravida 2, para 1 woman via normal spontaneous vaginal delivery. The woman had prenatal care with negative serologic findings. The infant is vigorous at birth with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. At approximately 30 hours after birth, she is hypothermic to 34.4°C with poor oral feeding, hypotonia, and tachypnea. Her glucose level is 32 mg/dL (1.78 mmol/L). A sepsis evaluation is performed, and ampicillin and gentamicin are started empirically. She is placed on high-flow nasal cannula for respiratory support and transferred to a nearby hospital for a higher level of care.

At approximately 34 hours after birth, the infant is noted to have coffee ground emesis, and she is in a clinical state of decompensation. She develops hepatomegaly, severe metabolic acidosis (base deficit -16), hyperkalemia (7.3 mEq/L [7.3 mmol/L]), and elevated creatinine concentration (1.52 mg/dL [134.4 μmol/L]). At approximately 45 hours, she develops bradycardia requiring intubation, chest compressions, and vasopressor support with 2 doses of epinephrine and initiation of a dopamine infusion. She is transferred to a tertiary referral center for further evaluation and management, given her continued clinical decline and severe metabolic derangements.

At approximately 49 hours after birth, she is noted to have hepatomegaly palpable to the level of the pelvis, delayed capillary refill, poor skin turgor, pale appearance, and hypotension. She has a potassium level of 7 mEq/L (7 mmol/L), and a rhythm strip shows ventricular tachycardia (Fig.). She is given calcium gluconate, nebulized albuterol, insulin, and dextrose containing fluids to address the hyperkalemia. Despite this, she has persistent stable ventricular tachycardia with blood pressures ranging from 50/30 to 70/50 mm Hg. In consultation with pediatric cardiology, intravenous lidocaine is started. Antibiotic coverage is broadened to ceftazidime, gentamicin, and acyclovir. She is found to have severe coagulopathy, with a prolonged prothrombin time of 61 seconds, international normalized ratio of 7.4, partial thromboplastin time of 93.3 seconds, and fibrinogen of 106 mg/dL (3.1 μmol/L). She remains severely acidotic (peak lactate >153 mg/dL (>17 mmol/L), base deficit of -24, and pH of 7.05) despite sodium bicarbonate boluses and a continuous infusion, as well as aggressive volume resuscitation with blood products. Her renal function worsens, with a peak creatinine concentration of 1.8 mg/dL (159 μmol/L) and elevated liver enzymes, including aspartate aminotransferase of 414 U/L (6.9 μkat/L), alanine aminotransferase of 84 U/L (1.4 μkat/L), and ammonia of 345 μg/dL (246 μmol/L). Because of concern for a metabolic disorder, additional studies are performed, with significantly abnormal α-fetoprotein of 76,800 ng/mL (76,800 μg/L)

**AUTHOR DISCLOSURE** Drs Schneider, DiBartolomeo, and Brennan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

and ferritin of 17,403 ng/mL (39,104 pmol/L). Pediatric hepatology is consulted, and intravenous immunoglobulin (IVIG) is initiated.

Because of a persistent coagulopathy, the infant receives continuous blood products, including 3 transfusions of fresh frozen plasma and 2 transfusions of cryoprecipitate. At approximately 60 hours after birth, bright red blood is noted coming from her endotracheal tube. With suctioning of the secretions, she develops bradycardia and experiences desaturation, which requires chest compressions. Copious and persistent bleeding is noted from the oropharynx and below the vocal cords upon visualization concerning for a pulmonary hemorrhage. After several doses of epinephrine, sodium bicarbonate, and calcium gluconate, there is no improvement in her cardiopulmonary status, and she dies approximately 1 hour later. The mother declines an autopsy.

Five days later, laboratory values show an elevated carnitine level of 47, acylcarnitine of 32, and abnormal newborn screening result.

## DISCUSSION

The infant described herein has the severe lethal neonatal form of carnitine palmitoyl transferase (CPT) deficiency type II. CPT II deficiency is a rare inborn error of metabolism. CPTs are essential enzymes for energy production via beta-oxidation of long-chain fatty acids, a carnitine-dependent process. Three distinct clinical forms of CPT II

deficiency have been noted—the common benign adult form characterized by exercise intolerance and myoglobinuria, an infantile form with variable outcomes, and a lethal neonatal form. (1)

The first case of the lethal neonatal form of CPT II deficiency was described by Hug et al in 1989. (1) This form typically presents within the first few hours or days after birth and is universally fatal. It is characterized by liver failure, hypoketotic hypoglycemia, respiratory distress, cardiomyopathy, cardiac arrhythmias, seizures, and lethargy. (2) It also can include facial abnormalities and structural malformations of the kidney and brain. (3) The myocardium, liver, and skeletal muscle rely on beta-oxidation, and as such, CPT II defects are most pronounced in these organ systems. (4) Our patient's initial presentation of encephalopathy was secondary to impaired fatty acid oxidation leading to profound hypoglycemia. The most commonly reported causes of death in neonatal CPT II deficiency are cardiac arrhythmias, respiratory failure, renal failure, or cardiomyopathy. The current case is unique in that none of the reported cases in the literature identify severe coagulopathy resulting in pulmonary hemorrhage as the cause of death.

At the time of death, neonatal hemochromatosis/gestational alloimmune liver disease (GALD) was at the top of our differential. Neonatal hemochromatosis is a form of liver injury that results from transplacental transfer of maternal antibodies against fetal hepatocyte antigens. (5) It is characterized by iron accumulation in the liver and other tissues,

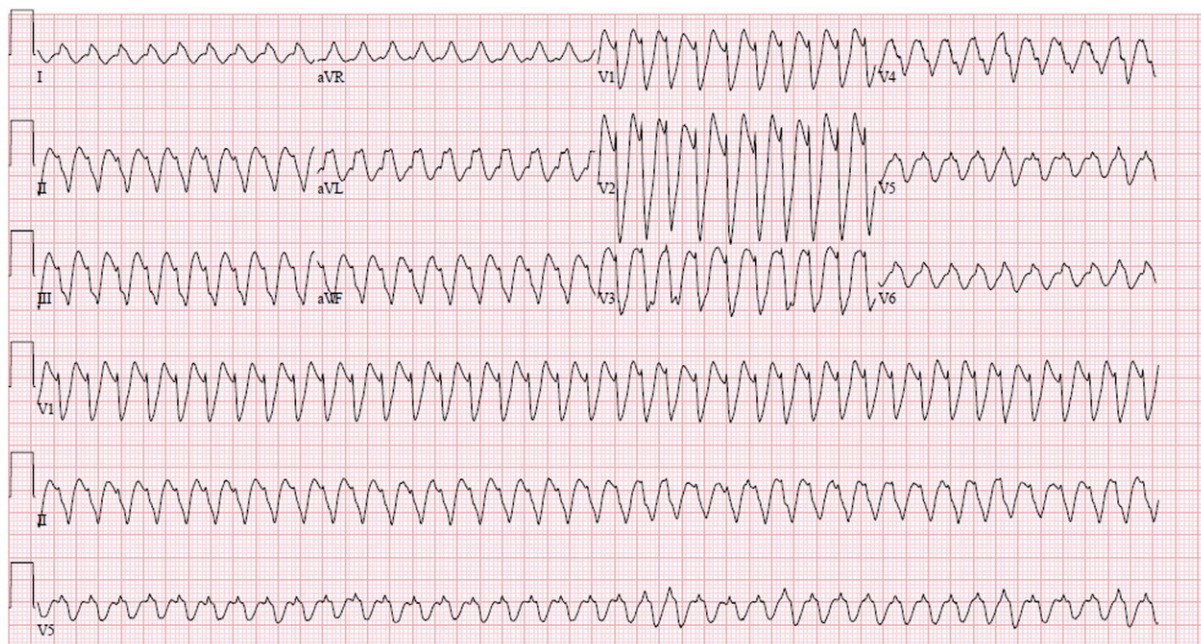


Figure. Rhythm strip with ventricular tachycardia.

resulting in hydrops, hepatomegaly, and ascites. Symptoms typically present in the first hours to days after birth with hypoglycemia, coagulopathy, hyperammonemia, hyperferitinemia, and elevated  $\alpha$ -fetoprotein levels. Because of the presence of these symptoms in our patient, an IVIG infusion was initiated. This patient had additional clinical findings such as arrhythmias, seizures, and renal failure, which are not typically associated with neonatal hemochromatosis. However, any time a neonate presents with liver failure, neonatal hemochromatosis/GALD must be high on the differential. (5)(6)

### Lessons for the Clinician

- CPT II deficiency is a rare inborn error of metabolism and can present in 3 forms—benign adult, variable infantile, and lethal neonatal.
- In neonates presenting with seizures, respiratory distress, cardiac dysrhythmias, liver failure, hypoglycemia, and unexplained coagulopathy, it is important to consider CPT II.
- The most commonly reported causes of death in neonatal CPT II deficiency are cardiac arrhythmias, respiratory failure, renal failure, or cardiomyopathy.
- CPT II shares common symptoms with neonatal hemochromatosis, so in any patient in whom liver failure and GALD is on the differential, IVIG therapy, which can be life-saving, should be initiated. (5)(6)

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids.

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# Index of Suspicion in the Nursery

## 2 A Newborn with a Changing Rash

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### PRESENTATION

A 39-week-gestation female infant is delivered by a 35-year-old gravida 3 woman. The neonate is born after an uneventful antenatal period, with a birthweight of 3,350 g; she is a product of a nonconsanguineous marriage. The mother has a history of 2 first-trimester abortions in the past. The infant is delivered via cesarean section in view of meconium-stained amniotic fluid with evidence of antenatal fetal distress. She is depressed at birth and needs bag and mask ventilation for 1 minute; her Apgar scores are 7, 9, and 9 at 1, 5, and 10 minutes, respectively.

The infant is admitted to the NICU in view of the respiratory distress and perinatal depression. She is cared for under a radiant warmer and needs oxygen support by hood for 3 days, following which, the respiratory distress resolves and the infant maintains saturation in room air.

On day 3 after birth, the infant is found to have multiple maculopapular erythematous rashes along with hyperpigmented nodules or plaques over bilateral upper and lower limbs (Fig 1). There is some desquamation, but lesions show absence of any associated vesicles or pustules. Morphologic findings of the skin lesion do not suggest any specific condition and it is a diagnostic dilemma. A senior dermatology consultation is obtained by the neonatology team. The team considers confluent erythema toxicum, nonbullous impetigo, neonatal herpes, and congenital candidiasis among the differential diagnoses at this point. The mother's genitals are examined again, but no vulvovaginal lesions are noted. Titers are sent for toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections for both the mother and infant, and the infant is started on antibiotics and feeding initiated.

On the eighth day after birth, the lesions progress to become more extensive in distribution and now involve the trunk along with bilateral upper and lower limbs. The lesions change to become vesiculobullous (Fig 2). The distribution of lesions becomes linear streak-like, along the lines of Blaschko (Fig 3). The possibility of an alternate diagnosis is mooted, considering the changing nature of the rash; a skin biopsy is performed.

Hematology evaluation of the infant and mother, including the blood culture and TORCH titers, is not suggestive. The biopsy report received on day 10 after birth reveals bullous lesions in the intraepidermal region, with spongiosis of surrounding keratinocytes. Bullous cavity shows collection of eosinophils with the presence of eosinophilic infiltrates in surrounding epidermis and focal prominence of dermal pigment incontinence (Fig 4). The infant has no seizure activity

**AUTHOR DISCLOSURE** Drs Pal, Jain, Chopra, and Singh have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





**Figure 1.** Maculopapular erythematous rashes with hyperpigmented nodules or plaques over bilateral upper limbs and lower limbs (Day 3).



**Figure 2.** Extensive distribution of lesions with emergence of vesicles and bullae (Day 8).

during the period of hospital stay, and ophthalmologic examination findings are normal. She is discharged, breastfeeding, on day 16 after birth. Lesions are still present at discharge though they have now been replaced by hyperpigmented brownish macules and papules (Fig 5).

## DISCUSSION

Based on the evolving morphology of the lesions and on the subsequent skin biopsy report, a diagnosis of incontinentia pigmenti (IP) is made.

### The Condition

IP or Bloch-Sulzberger syndrome is a rare X-linked dominant disorder with an estimated prevalence of 0.2 in 100,000 infants, in which changes in skin and its appendages are

present combined with other organs including the central nervous system (CNS). IP appears almost exclusively in girls and is usually lethal in boys. (1) *IKBKG* (previously *NEMO*) is the gene known to be associated with IP. (2)

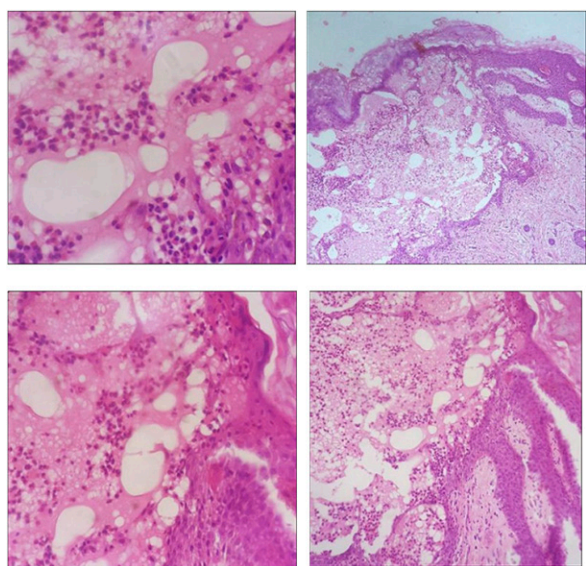
Skin changes, often the first observed clinical sign of IP, typically occur during the first weeks of age to adulthood along Blaschko lines, (2) typically in 4 stages. Onset and duration of stages vary and the stages may overlap. Not all patients experience all stages. Each stage has characteristic morphologic and histopathologic findings. (3)

- Stage 1 (vesiculobullous stage): This stage presents within the first 2 weeks of age in 90% of patients, with erythematous blisters grouped along the lines of Blaschko. Histopathology reveals spongiosis and intraepidermal vesicles containing eosinophils, with many apoptotic keratinocytes in the epidermis.



**Figure 3.** Change of distribution of lesions to linear pattern along lines of Blaschko (Day 9).

- **Stage 2 (verrucous stage):** This occurs in about 70% of patients usually within 2 months and disappears by 6 months of age. Hyperkeratotic verrucous papules and



**Figure 4.** Skin biopsy with bullous lesions in intraepidermal region with spongiosis of surrounding keratinocytes. The bullous cavity is showing collection of eosinophil with presence of eosinophilic infiltrates in surrounding epidermis with focal prominence of dermal pigment incontinence suggestive of Incontinentia pigmenti (Day 9).



**Figure 5.** Hyperpigmented brownish macules and papules (Day 16).

plaques develop over the healing blisters. Histopathology shows papillomatosis, hyperkeratosis, and acanthosis of the epidermis. Major melanin incontinence is seen in this stage.

- **Stage 3 (hyperpigmented stage):** This is the hallmark of IP, experienced by nearly 98% of patients. Pigmentation ranges from blue-grey to brown, occurs in streaks or whorls, develops within the first few months of age, and fades by adolescence. Marked melanin incontinence, numerous melanophages in the dermis, no epidermal hyperplasia, and scattered apoptotic cells in the epidermis are some of the characteristic histopathologic findings.
- **Stage 4 (atrophic/hypopigmented stage):** This occurs in adolescence and persists into adulthood. It can be identified by pale, hairless patches or streaks found mostly on the lower legs. An atrophic epidermis can be seen with massively reduced melanin in the basal layer, with persistence of apoptotic bodies in the epidermis or papillary dermis. On biopsy, pilosebaceous units and eccrine glands are completely absent at this stage.

## Diagnosis

Criteria for the diagnosis of IP were listed by Landy and Donnai in 1993. (1) Skin manifestations in IP represent the



major criteria for its diagnosis. Our patient had 2 major criteria for diagnosis of IP. An update to these diagnostic criteria was proposed in 2014 by Minić et al, (4) who suggested including genetic testing and histopathologic findings as additional diagnostic criteria, along with many others. Genetic testing could not be conducted in our case.

### Monitoring and Follow-up

The disease progresses to affect several organs including the skin and hair, CNS, eye, oral cavity, and teeth. CNS anomalies are the most serious complications of IP. (5) CNS anomalies may also manifest from the neonatal period up to early infancy. (6) According to serial reports, 13% to 35% of patients with IP had CNS anomalies in the form of seizures, motor impairment, intellectual disability, and microcephaly. (7)(8)

### Lessons for the Clinician

- A rash in the newborn period may have several differential diagnoses, and the prognostic implications for each are different.
- A rash with a changing nature in a neonate should alert the clinician to keep a high index of suspicion for this condition.
- Careful examination of the newborn for the nature, distribution, and progression should be undertaken serially and with relevant laboratory tests to differentiate it from other causes such as impetigo, neonatal herpes, and congenital syphilis.
- A rash in a female infant that occurs in a streak or whorl pattern along Blaschko lines should be considered for IP and a skin biopsy could aid in the diagnosis.
- All neonates with IP may not adhere to the timeline of progression over different stages. The time of presentation of the different stages markedly varies, and an overlap between stages may be noted.

- Once diagnosed with IP, neonates need to receive long-term follow-up to look for abnormalities of other organs.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the differential diagnosis and syndromes associated with hyperpigmented lesions, including cafe au lait spots, Peutz-Jeghers syndrome, giant hairy nevus, incontinentia pigmenti, and pigmented nevi.

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## 3

## Sudden Unexpected Collapse in a Full-term Infant

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### PRESENTATION

A 3,040-g appropriate-for-gestational age girl is delivered vaginally at 38 weeks by an 18-year-old primigravida following induction of labor for preeclampsia. Pregnancy complications included obesity and elevated maternal serum  $\alpha$ -fetoprotein without open neural tube defect on ultrasonography. The mother had received 2 g/hour of magnesium sulfate during labor. The infant's Apgar scores are 8 and 9 at 1 and 5 minutes, respectively, and she requires routine postdelivery care. The resuscitation team notes normal physical examination findings, including appropriate tone and intact spine, and the infant remains with her mother. At 90 minutes after birth, she is lying skin to skin on her mother's chest after attempting breastfeeding and is found by her nurse to be pale, limp, and apneic. She is placed on a radiant warmer, positive pressure ventilation is initiated, and the NICU team is called.

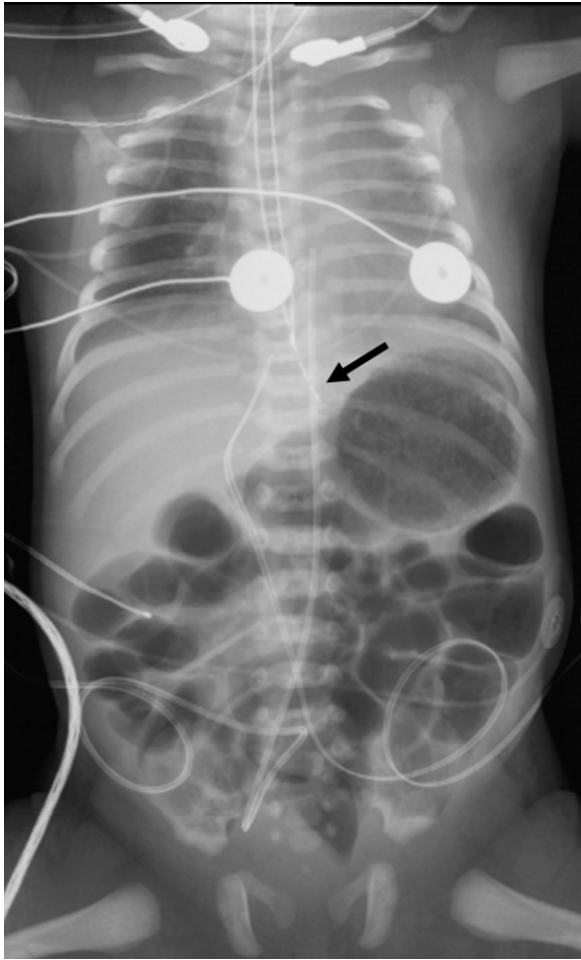
On arrival, the NICU team finds the neonate to have cyanosis, hypotonia, and apnea. Her heart rate is 60 beats/min. Despite improvement with positive pressure ventilation, the infant requires intubation for persistent apnea. On physical examination, she is stuporous with no spontaneous activity, and has absent primitive reflexes, flaccid tone, and sluggish pupils. She is admitted to the NICU for management of respiratory failure and neonatal encephalopathy. Her initial arterial blood gas demonstrates severe metabolic acidosis (pH 7.00/pCO<sub>2</sub> 35/pO<sub>2</sub> 124/HCO<sub>3</sub> 9/base deficit -23, lactate 14.9 mg/dL [1.7 mmol/L]). Comprehensive metabolic panel is normal except for low serum carbon dioxide (14 mEq/L [14 mmol/L]) and elevated magnesium (4.7 mg/dL [2.35 mmol/L]). She receives mechanical ventilation and whole-body therapeutic hypothermia is initiated. Umbilical lines are placed. She receives antibiotics for suspected sepsis; blood culture remains negative. Metabolic acidosis resolves after she receives normal saline and sodium bicarbonate boluses. Complete blood cell count is significant only for mild anemia (hemoglobin 11.5 g/dL [115 g/L]). Serum ammonia is normal. Cranial ultrasonography shows no acute hemorrhage. Echocardiography demonstrates normal structure and biventricular function.

### DISCUSSION

#### Progression

At 18 hours after birth, the neonate's abdomen becomes distended, and a 10F Replogle suction tube is placed, which has a nonbilious output of less than 10 mL/kg per day. Figure 1 depicts the abdominal radiograph after Replogle tube placement.

**AUTHOR DISCLOSURE** Drs Aghion, Falck, and Sundararajan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



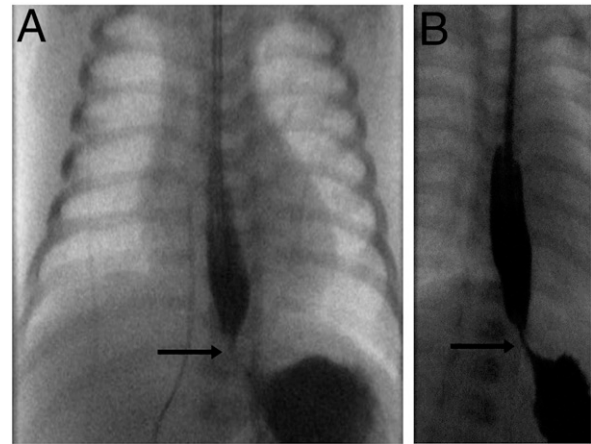
**Figure 1.** Chest and abdominal radiograph showing the tip of the Replogle tube terminating above the gastric bubble (black arrow) with diffuse gaseous distention of the bowel.

### Differential Diagnosis

- Airway obstruction due to:
  - Accidental suffocation
  - Hypotonia due to hypermagnesemia
- Aspiration secondary to:
  - Esophageal stricture
  - Esophageal web
  - Esophageal atresia
  - Neonatal achalasia

### Diagnosis

The infant undergoes therapeutic hypothermia for 72 hours and is extubated on day 2 after birth. The Replogle tube remains malpositioned above the stomach. Upper gastrointestinal contrast study on day 6 after birth shows **fixed narrowing at the gastroesophageal (GE) junction**, which is concerning for stenosis (Fig 2A). Upper gastrointestinal endoscopy and esophageal dilation are performed on day 10 after birth, ruling out atresia and making stricture less



**Figure 2.** A. Upper gastrointestinal contrast study illustrates the fixed narrowing at the gastroesophageal junction (black arrow) concerning for stenosis. B. Esophagogram obtained after esophageal dilation illustrating the persistent severe narrowing (**bird's beak appearance**) at the gastroesophageal junction (black arrow), despite contrast now passing readily into the stomach, suggestive of **neonatal achalasia**.

likely. Subsequent esophagography on day 13 after birth shows persistent severe narrowing at the GE junction (Fig 2B) concerning for neonatal achalasia. On day 15 after birth, esophagogastroduodenoscopy is performed. Biopsy of the GE junction shows minimal inflammation of the distal esophagus. Repeat esophagography on day 29 after birth continues to demonstrate persistent severe narrowing at the GE junction consistent with neonatal achalasia. The infant undergoes laparoscopic **Heller myotomy** on day 34 with complete symptom resolution. She is discharged 6 weeks after birth on full oral feeds. At her 6-month NICU follow-up visit, neurodevelopmental screening result is normal. Sudden unexpected collapse is presumed to be because of aspiration during the first breastfeeding attempt secondary to obstruction of the lower esophageal sphincter (LES) from neonatal achalasia. In the presence of this confirmed anomaly, potential etiologies such as **accidental suffocation** and hypotonia are less likely to be the primary cause of this event. We believe this is the first report of neonatal achalasia presenting as **sudden unexpected collapse in the immediate newborn period**.

### The Condition

**Neonatal achalasia** is a neuromuscular disorder of esophageal motility characterized by **failure of relaxation of the distal esophagus**. (1)(2) Achalasia occurs in 0.5 to 1 in 100,000 infants; it is uncommon in children (3%–5%) and extremely rare in neonates (<0.5%). (2)(3) Achalasia is associated with conditions such as trisomy 21, congenital hypoventilation syndrome, eosinophilic

esophagitis, familial dysautonomia, and achalasia-alacrima-adrenocorticotrophic hormone insensitivity syndrome. (1) The pathophysiology involves deterioration of the inhibitory myenteric plexus innervating the LES and esophageal body. (1) This creates a disparity between inhibitory and excitatory neurons, leading to absent peristaltic activity in the esophageal body, elevated LES resting pressures, and lack of LES relaxation with swallowing. (1) Clinical presentation typically includes **emesis, recurrent aspiration pneumonia, nocturnal cough, hoarseness, and feeding issues.** (1)(2)(4) Neonates with achalasia could also present with feeding difficulties shortly after birth that result in **sudden unexpected** collapse from pooled secretions as occurred in our infant.

Acute cardiorespiratory compensation resulting in sudden unexpected collapse could also represent a symptom of a previously undiagnosed condition, such as congenital heart disease, pulmonary hypertension, pneumonia, inborn error of metabolism, or hypermagnesemia from maternal medication. (5)(6) The other listed diagnoses were excluded with radiography, echocardiography, and serial laboratory blood tests. The episode of unexpected collapse occurred under clinical observation while the mother was attempting to breastfeed her infant with nursing assistance, therefore, accidental suffocation or foul play was excluded as a possible etiology. Membranous esophageal atresia, an extremely rare subtype of esophageal atresia could also present with drooling of saliva and frothing in the early newborn period. (7) However, radiologic findings will include paucity of bowel gas on plain radiography with demonstration of an atretic esophageal pouch on esophageal contrast study. (7)

Confirmatory diagnostic studies for achalasia include fluoroscopic examinations, such as modified barium swallow or esophagography, and esophageal manometry. Esophagography findings include a dilated proximal esophagus with classic **"bird's beak"** tapering of the distal esophagus. (1)(2)(4) Esophageal manometry demonstrates elevated resting LES pressure, absent or low-amplitude peristalsis, or nonrelaxing LES on swallowing. (1)(2) Medical management includes **nifedipine, botulinum injection, or pneumatic dilation.** (1)(4) Surgical options for achalasia include **laparoscopic Heller myotomy**, in which the esophageal muscle is longitudinally incised approximately 5 cm above the GE junction, extending 2 to 3 cm into the cardia of the stomach, (1)(4) or per oral endoscopic myotomy, with the youngest reported patient being 3 years old. (1) In conclusion, neonatal achalasia, a rare entity in

infants, requires a high index of suspicion for diagnosis in the immediate newborn period. Prompt early diagnosis and surgical treatment of the mechanical obstruction is curative.

### Lessons for the Clinician

- Achalasia is a neuromuscular esophageal disorder that is uncommon in infancy and may occur in isolation or with other anomalies or syndromes.
- Symptoms of achalasia typically include feeding intolerance, vocalization abnormalities, and recurrent aspiration. An atypical symptom is feeding difficulty soon after birth that could result in sudden unexpected collapse from pooled oral secretions.
- Diagnosis is confirmed in neonates and children via esophagography.
- Treatment options include medications, pneumatic dilation, and surgical management with laparoscopic Heller myotomy.

## American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Breastfeeding.
- Know the indications for assisted ventilation, including continuous positive airway pressure, immediately after birth and how to assess its effectiveness.
- Know the factors affecting and regulating the systemic circulation in the fetus (including umbilical vessels) and newborn infant during the perinatal transitional period.

### ACKNOWLEDGMENT

We would like to thank Dr Jane S. Kim at University of Maryland School of Medicine for her assistance with the diagnostic radiology studies.

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## Torsed or Not?

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### ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

#### Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

### DEFINITIONS

#### Baseline FHR

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

#### Baseline Variability

- Fluctuations in the baseline FHR of  $\geq 2$  cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute

**AUTHOR DISCLOSURE** Drs Anwar and Spiel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. Arterial Umbilical Cord Gas Values

	pH	Pco <sub>2</sub> (mm Hg)	Po <sub>2</sub> (mm Hg)	BASE EXCESS
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤-10 (-2.0 to -9.0)
Respiratory acidosis	<7.20	>60	Variable	≤-10
Metabolic acidosis	<7.20	<60	Variable	≥-10
Mixed acidosis	<7.20	>60	Variable	≥-10

\*Normal ranges from Obstet Gynecol Clin North Am. 1999;26:695.

#### • Classification of variability:

Absent: Amplitude range is undetectable

Minimal: Amplitude range is greater than undetectable to 5 beats/min

Moderate: Amplitude range is 6–25 beats/min

Marked: Amplitude range is >25 beats/min

#### Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

#### Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

#### Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

#### Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

#### Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline

- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent

#### Sinusoidal FHR Pattern

- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes

#### Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes
  - Normal: ≤5 contractions in 10 minutes
  - Tachysystole: >5 contractions in 10 minutes

#### Interpretation

A 3-tier FHR interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability

- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecol*. 2008;112:661-666 and American College of Obstetricians and Gynecologists. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *ACOG Practice Bulletin No. 106*. Washington, DC: American College of Obstetricians and Gynecologists; 2009.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

## CASE PRESENTATION

A 31-year-old gravida 1 woman presented to her obstetrician's office at 28 weeks and 2 days of gestation with sudden onset of severe 10/10 left-sided flank pain, abdominal pain, nausea, and vomiting. Her pregnancy was dated by the last menstrual period consistent with a first-trimester ultrasound scan.

She had a known left ovarian simple cyst that was last measured as 4 cm in size on ultrasonography 2 months earlier. Given the sudden onset of pain in the setting of a known ovarian cyst, she was sent to labor and delivery for further evaluation. She had an evaluation at an outside institution including normal renal ultrasonography findings, white blood cell (WBC) count of  $13,600/\mu\text{L}$  ( $13.6 \times 10^9/\text{L}$ ), and a pelvic ultrasound scan with "5.4-cm paraovarian cyst with abnormal spectral analysis" with concern for ovarian torsion. She received intravenous narcotics for pain and was transferred for tertiary care.

Her medical history was notable for a prior hysteroscopic polypectomy, but she was otherwise healthy, without known comorbidities. Her prenatal course was otherwise uncomplicated except for approximately 1 month before this presentation, when she had another episode of pain that was attributed to round ligament pain at the time.

## CASE PROGRESSION

Upon arrival at the tertiary facility, she denied any loss of fluid, contractions, or vaginal bleeding. Her blood pressure, heart rate, and oxygen saturation were normal. Her abdominal examination was notable for a gravid and nondistended abdomen. She had significant left lower quadrant and left flank tenderness to palpation. There was no rebound tenderness; guarding was present. Bimanual examination elicited left adnexal tenderness to palpation, without fundal tenderness. Preterm premature rupture of membranes was ruled out on speculum examination. Her cervix was long, closed, firm, and posterior. She received 2 mg of intravenous hydromorphone for analgesia. A representative FHR tracing is displayed in Fig 1.

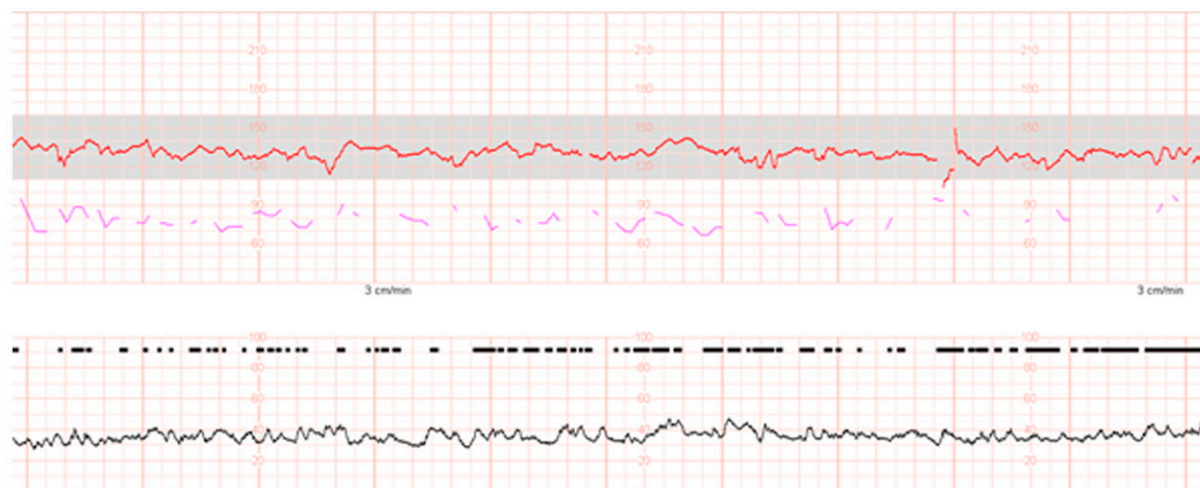


Figure 1. External fetal monitoring strip 1.

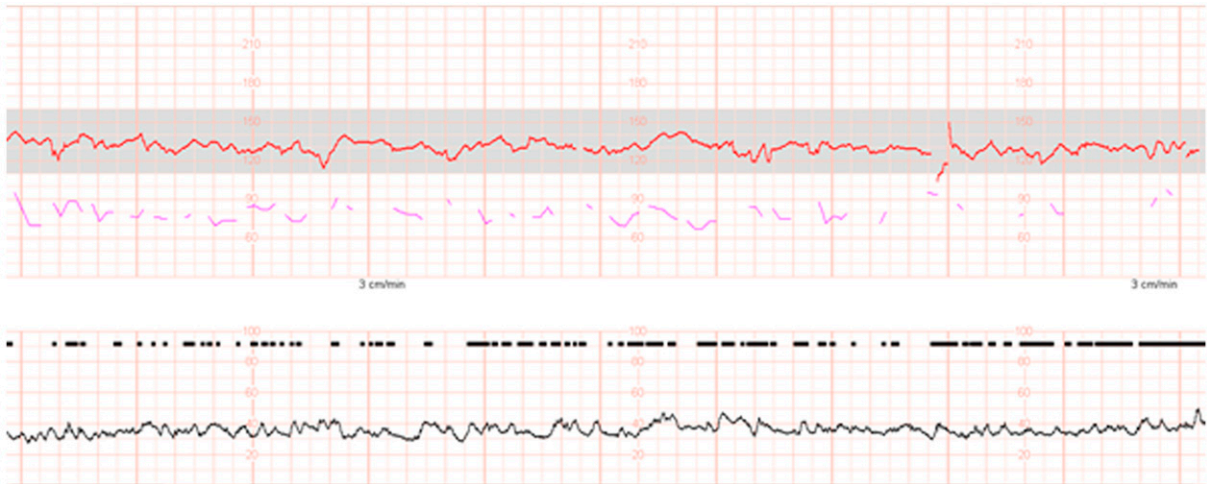


Figure 1. External fetal monitoring strip 1.

#### Interpretation of Fig 1:

- Variability: Moderate.
- Baseline rate: 120 beats/min.
- Episodic patterns: None.
- Periodic patterns: None.
- Uterine contractions: Irritable.
- Interpretation: Reactive and reassuring.
- Differential diagnoses: Abruption, preterm labor, infection, or normal pregnancy.
- Action: The physician was notified and ongoing continuous monitoring was performed.

At this time, the differential diagnosis included preterm labor, renal colic from nephrolithiasis, ovarian torsion, concealed abruption, pancreatitis, and small bowel obstruction. Her complete blood cell count was notable for a WBC count of  $16,500/\mu\text{L}$  ( $16.5 \times 10^9/\text{L}$ ) with a leftward shift, with otherwise normal cell counts (a slight change from the outside institution). Basic metabolic panel, liver function tests, lipase, and total bilirubin were normal. Fetal fibronectin was negative. Urinalysis was negative for red blood cells, WBCs, nitrites, crystals, or ketones. Left renal ultrasonography showed no evidence of a kidney stone. Pelvic ultrasonography showed a 5.4-cm paraovarian cyst, and the reading radiologist commented that torsion could not be ruled out.

The history, physical examination, and imaging findings were highly suggestive of ovarian torsion, despite lack of definitive imaging evidence. The patient was counseled to undergo surgical exploration to rule out ovarian torsion; an ovary with torsion could lead to ovarian necrosis, infection, preterm labor, and sepsis,

as well as loss of ovarian function. Given her advanced gestational age and size of the uterus, diagnostic laparoscopy was not recommended because of likely suboptimal evaluation; instead exploratory laparotomy was deemed the most prudent course of action. Her consent was obtained for an exploratory laparotomy, for possible cyst drainage, ovarian detorsion, left oophorectomy, salpingectomy, and left salpingo-oophorectomy. Given the preterm gestational age, the patient participated in discussion with maternal-fetal medicine and neonatology regarding neonatal and obstetrical outcomes. She received betamethasone for fetal benefit in preparation for possible preterm labor or urgent need for delivery. The patient and the medical team opted for intraoperative fetal monitoring to ensure adequate monitoring of placental perfusion and hemodynamic status. She was informed that should her fetus develop a nonreassuring FHR tracing, cesarean delivery might be indicated, and after extensive discussion, she elected to proceed with the aforementioned procedure.

The patient was taken to the operating room, prepared, and draped in the normal sterile fashion. Ultrasonography was performed preoperatively for surgical incision mapping. She was positioned in a rightward tilt to improve visualization of the left pelvic sidewall. A vertical midline incision was made inferior to the umbilicus and extending around the umbilicus. Upon adequate visualization of the uterus and adnexa, a sterile FHR monitor was placed directly on the skin, to perform continuous fetal monitoring. Inspection of the left adnexa revealed a blue-purple ovary and a 5-cm left paratubal simple cyst. Left ovary torsion occurred 3 times at the utero-ovarian ligament and once at

the infundibulopelvic ligament. The left paratubal cyst was brought up to the skin incision and drained for clear fluid without spillage into the abdominal cavity. Detorsion of the ovary was possible. However, the paratubal cyst occupied a large surface area along the fallopian tube, necessitating a partial left salpingectomy to safely remove the cyst without additional bleeding. Afterwards, the left ovary showed color changes consistent with viable ovarian tissue, indicating revascularization. Ovarian perfusion continued to improve, illustrated by progressive healthy color

change. Given the patient's desire for preserved ovarian function and improvement of ovarian revascularization after detorsion, oophorectomy was deferred. Subsequently, the ovary was replaced into the pelvic cavity, and the abdominal cavity was closed in the usual fashion. Fetal testing throughout the case was reassuring, with a fetal baseline between 130 and 140 beats/min, showing moderate variability. No fetal decelerations were appreciated during the case, as shown in the FHR tracing in Fig 2.

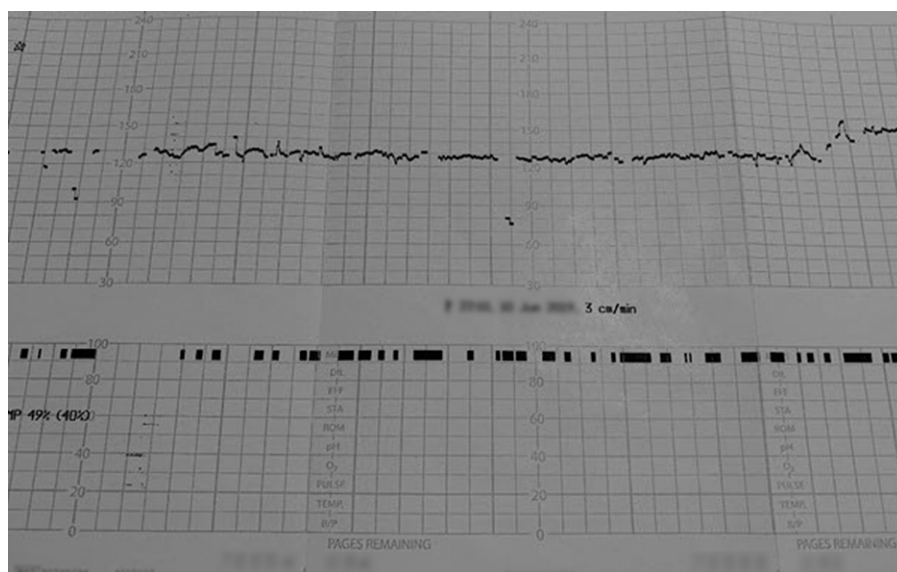


Figure 2. External fetal monitoring strip 2.



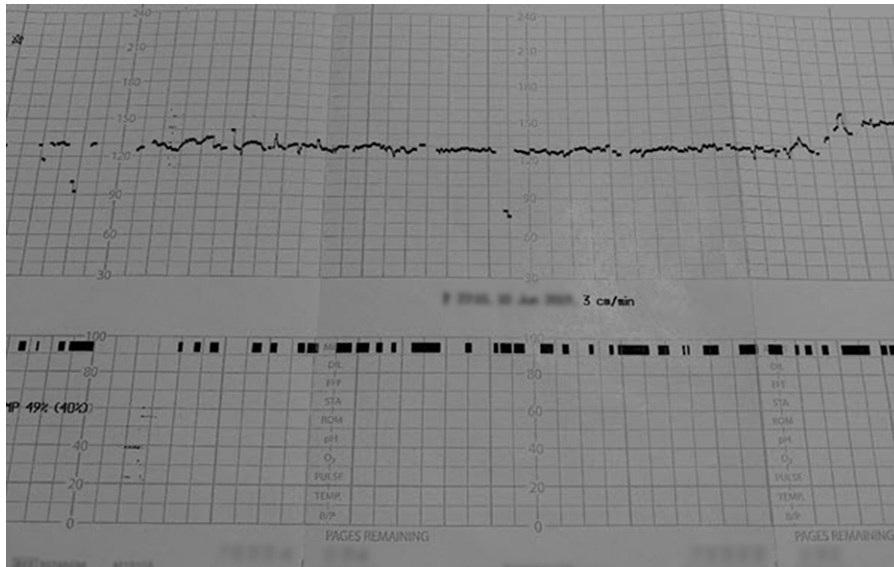


Figure 2. External fetal monitoring strip 2.

Interpretation of Fig 2:

- Variability: Moderate.
- Baseline rate: 130 beats/min.
- Episodic patterns: None.
- Periodic patterns: None.
- Uterine contractions: Not monitored intraoperatively.
- Interpretation: Reassuring.
- Differential diagnosis: Adequate uterine perfusion.
- Action: Continued intraoperative fetal monitoring.

## OUTCOME

The patient was taken to labor and delivery for postoperative recovery. She was observed for 12 hours after the procedure with continuous external FHR monitoring and tocometry. Her original pain had resolved by this time. Her FHR tracing was appropriate for gestational age throughout the postoperative monitoring process, and she did not develop preterm labor. The representative FHR tracing is shown in Fig 3.

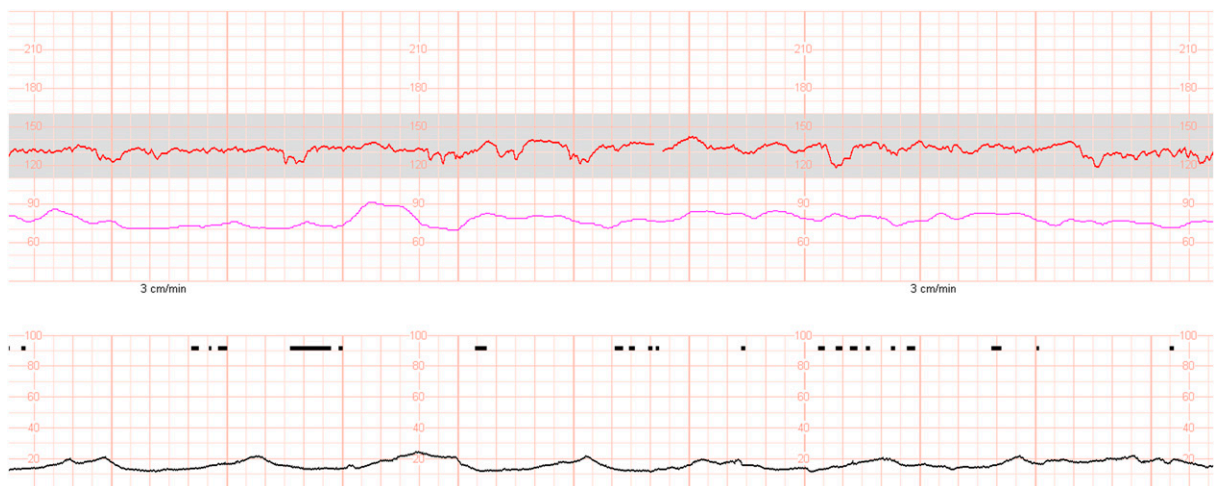


Figure 3. External fetal monitoring strip 3.

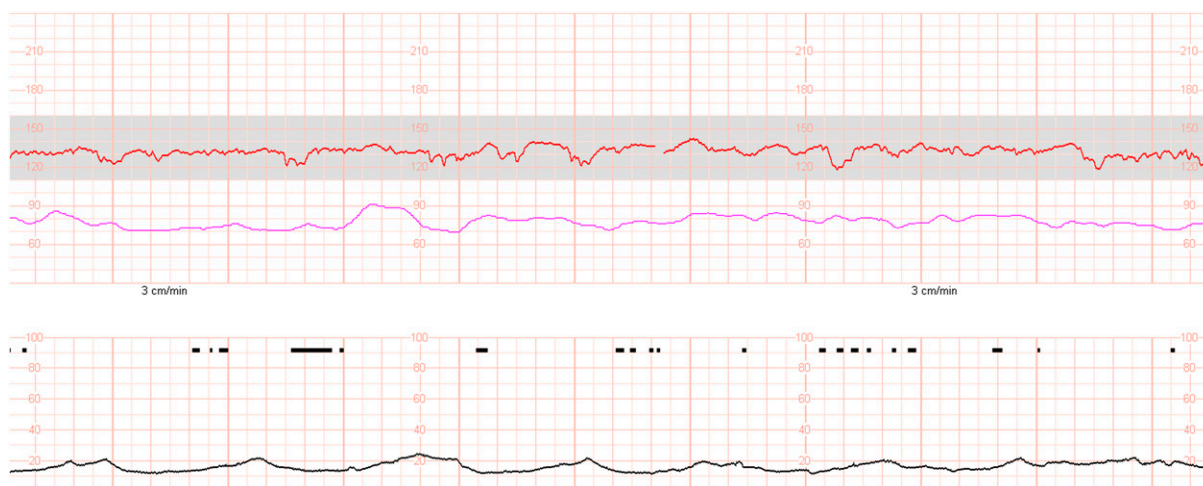


Figure 3. External fetal monitoring strip 3.

#### Interpretation of Fig 3:

- Variability: Moderate.
- Baseline rate: 130 beats/min.
- Episodic patterns: None.
- Periodic patterns: None.
- Uterine contractions: Irritability.
- Interpretation: Reassuring.
- Differential diagnosis: Irritability can suggest preterm labor, abruption, infection, dehydration, or normal variant in the setting of recent surgery.
- Action: The physician was notified. Given that the patient was not feeling the contractions, and the FHR tracing was overall reassuring, the patient was hydrated with intravenous fluids and the contractions improved.

After 12 hours of reassuring prolonged monitoring, the patient was then observed on the antepartum service with daily fetal nonstress testing, and discharged on postoperative day 2, with a plan for follow-up with her primary obstetrician. Her prenatal care was transitioned back to her primary obstetrician. Pathology result showed a serous cyst, peritoneal surfaces with stromal decidualization, and an unremarkable fallopian tube. She had no further episodes of pain or recurrence of torsion in pregnancy.

## DISCUSSION

Torsed or not? This is a common clinical question that obstetricians and gynecologists face when evaluating a woman with acute-onset pelvic pain, especially in the setting of a known adnexal mass. Ovarian torsion is a rare complication of pregnancy, with an incidence of 1 to 5 per 10,000 pregnancies. (1) The clinical diagnosis of ovarian torsion is challenging enough in

nonpregnant women, but it poses even greater diagnostic difficulty in pregnant women, because the enlarged, gravid uterus makes the ovaries difficult to identify on ultrasonography. When torsion is identified, it is imperative to proceed promptly with surgical intervention to rescue vulnerable ovarian tissue, because compromise of vascular supply can be swift and consequential if untreated. Despite the associated risks of untreated or under-treated ovarian torsion in the pregnant population, clinicians may be more likely to manage expectantly. In fact, in a cohort study evaluating treatment patterns in 1,366 pregnant women with ovarian torsion compared with matched nonpregnant patients with torsion, pregnant patients were more likely to be treated nonsurgically than nonpregnant women (57.04% vs 50.97%; odds ratio 1.18; confidence interval 1.08–1.51;  $P < .1$ ). (1)

Traditionally, laparoscopy has been the preferred method of intervention in both pregnant and nonpregnant women. However, a retrospective review of ovarian torsion in pregnant and nonpregnant women between 2003 and 2011, using the National Inpatient Sample, found that laparotomy was the most common treatment in both pregnant and nonpregnant women, with the frequency being slightly higher in the former group. (2) In a study by Ginath et al, (3) which compared outcomes and treatment approaches in patients with torsion based on pregnancy status, all patients underwent detorsion. Of these, 84% of the nonpregnant women and 67% of the pregnant women received an additional procedure, including cystectomy, fixation, unilateral or bilateral salpingo-oophorectomy, salpingectomy, or puncture. Despite hesitancy regarding what is considered invasive intervention during pregnancy, the 2011 guidelines regarding laparoscopy during pregnancy from the Society of American Gastrointestinal and Endoscopic Surgeons recommend laparoscopy when indicated, such as with torsion. (4) Laparoscopy

is considered safe during pregnancy, regardless of trimester, with minimal associated morbidity and mortality for both the fetus and the mother. Guidelines explicitly recommend this surgical modality for both diagnosis and treatment when clinical suspicion is high, as in our case, reinforcing the need for timely intervention when indicated.

In the United States, 75,000 pregnant women undergo antepartum surgical procedures every year. (5) Because of limited evidence, many practitioners diverge on the stance of evaluation of fetal well-being during nonobstetric surgery. Although the need for pre- and postoperative assessment of FHR has been proposed and widely accepted by most, there is no consensus regarding intraoperative FHR monitoring. The American College of Obstetricians and Gynecologists (ACOG) states that the decision to use intraoperative FHR monitoring needs to be individualized, based on gestational age, type of surgery, and the resources available at the institution. According to ACOG, intraoperative electronic fetal monitoring may be appropriate if the following criteria are met: viable fetus, physically possible to perform intraoperative fetal monitoring, health care clinician with obstetric privileges is available to intervene on a nonreassuring tracing, and the woman provides consent for emergency cesarean delivery for fetal indications. (6) In addition, the committee opinion also clarifies that monitoring should only be performed during a procedure that could allow for safe interruption and alteration of the procedure to perform emergency delivery. (6)

Interestingly, a systematic review of 41 women undergoing antepartum nonobstetric surgery at 22 weeks gestation or greater with use of intraoperative FHR monitoring found that cesarean delivery was not required for any case with nonreassuring intraoperative FHR findings. (7) In the cases that had a nonreassuring result on intraoperative FHR monitoring, this was explicable because of maternal etiology (no cases of nonreassuring intraoperative FHR monitoring were seen with stable maternal vital signs). Five percent of women required delivery within 48 hours postoperatively because of nonreassuring intraoperative FHR monitoring. Nonreassuring intraoperative FHR tracing was defined as NICHD category II or III characteristics. (7)

When interpreting the FHR tracing, it is important to keep in mind the effects of general anesthesia on the fetus. According to Reitman and Flood, (8) regional anesthesia is preferred over general anesthesia whenever the surgery permits. Because all general anesthetic drugs cross the placenta, loss of FHR variability may not necessarily be due to fetal distress but rather due to anesthetic effects on the fetal autonomic nervous system. A more specific marker for fetal

hypoxemia and acidosis is a slowing of the FHR, rather than a decrease in variability. (8) Although decrease in temperature and maternal respiratory acidosis are known causes of fetal bradycardia, anesthetic agents should be considered in the differential. (8)

In summary, the patient in this case met the criteria to undergo intraoperative FHR monitoring, which was reassuring throughout the procedure and helped with providing hemodynamic management for the mother. The decision to proceed with exploratory laparotomy was prudent because it enabled identification, detorsion, and preservation of the ovary at this later gestational age. Preservation of the ovary prevented peritonitis, spontaneous abortion, preterm delivery, and death, which have been associated with ovarian infarction and/or gangrenous adenexa. (4) Although the prospect of operating on a gravid woman is a daunting task that is quick to give pause to any physician, it is imperative to provide the same management for ovarian torsion regardless of pregnancy status. Successful outcomes, such as in this case, are a reminder that while caution is advised before performing unnecessary procedures in pregnancy, performing an indicated surgery is necessary to ensure the health of the mother and fetus. This case is important because it demonstrates that intraoperative fetal monitoring can be successful and should be considered for potentially viable fetuses. Further, this case demonstrates that adverse outcomes can be avoided when prompt recognition, counseling, coordination of care, and surgery are performed in pregnancy.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Understand the rationale, interpretation, and limitations of maternal detection of fetal movement, of the biophysical profile, the non-stress test, and the contraction stress test as means of assessing fetal well-being.

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## An Extremely Premature Newborn with Cutaneous Lesions

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### THE CASE

An extremely premature 9-day-old female infant in the NICU developed 2 circular lesions on her back. The lesions quickly progressed to a necrotic ulcer.

### Prenatal and Birth Histories

- Born to a 19-year-old gravida 2, para 1 white woman
- Prenatal course was complicated by bleeding in the second trimester, which resolved, and by maternal hemorrhage, which precipitated delivery
- Estimated gestational age: 23 weeks
- Emergent cesarean section for maternal hemorrhage and concern for placental abruption
- Prenatal maternal laboratory tests: Group B *Streptococcus* unknown; hepatitis B virus surface antigen negative; human immunodeficiency virus negative; gonorrhea negative; chlamydia negative; rubella immune; syphilis negative
- Apgar scores: 2, 3, and 5 at 1, 5, and 10 minutes, respectively
- Delivery room course: Infant required positive pressure ventilation followed by intubation and administration of surfactant

### Presentation

At 9 days of age, the infant's bedside nurse noted 2 small lesions on her lower back; one was 1 cm in diameter, and the other was slightly smaller. The lesions initially had a red raised border with a white center (Fig 1A), but over 24 hours, the centers of the lesions became black (Fig 1B).

### PROGRESSION

#### Vital Signs

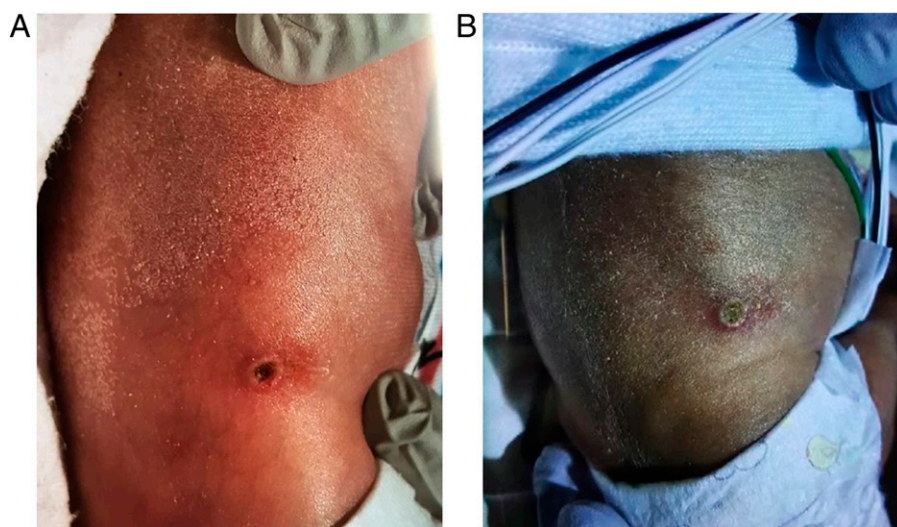
- Heart rate: 181 beats/min
- Respiratory rate: 39 breaths/min
- Blood pressure: 64/44 mm Hg
- Oxygen saturation: 81% with fraction of inspired oxygen of 0.35 via synchronized intermittent mechanical ventilation
- Temperature: 98.8°F (37.1°C) measured by axillary route

#### Physical Examination (10 days of age)

- Birthweight: 655 g (92nd percentile); length: 32 cm (96th percentile)
- Current weight: 650 g

**AUTHOR DISCLOSURE** Drs Olivero, Caulfield, and Fulton have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.





**Figure 1.** A. Initial appearance of circular cutaneous lesion on right flank of extremely premature infant. B. Right flank lesion that evolved to central necrosis over a 24-hour period.

- Head: Normocephalic with a soft and flat anterior fontanelle
- Eyes: Eyelids fused
- Oral cavity: Oral intubation
- Lungs: Symmetric ventilated breaths heard bilaterally without focal decrease in aeration of adventitious sounds
- Cardiovascular: Sinus tachycardia, 2/6 holosystolic murmur heard throughout precordium
- Abdomen: Soft, nondistended, no masses or hepatosplenomegaly appreciated
- Genitourinary: Normal external premature female genitalia
- Skin: Round lesion of 1-cm diameter on right lower back with a mildly erythematous border and black center; lesion is indurated but with no fluctuance; similar-appearing 0.5-cm lesion noted on left lower back
- Musculoskeletal: No edema or deformity
- Neurologic: Reactive to examination, moves all 4 extremities spontaneously

#### Laboratory Studies

- White blood cell (WBC) count:  $16,530/\mu\text{L}$  ( $16.5 \times 10^9/\text{L}$ ) with 64% neutrophils, 13% lymphocytes, 22% monocytes, 1% eosinophils
- Hemoglobin: 11.5 g/dL (115 g/L)
- Platelet count:  $173 \times 10^3/\mu\text{L}$  ( $173 \times 10^9/\text{L}$ )
- C-reactive protein: 0.4 mg/L (3.8 nmol/L)
- Peripheral blood culture: No bacteria or yeast isolated at 5 days of growth
- Wound Gram stain and culture: Few WBCs and few Gram-positive cocci per low-power field, normal skin flora isolated at 5 days of growth

- Fungal stain and culture from superficial swab of lesion: No fungal elements observed, no fungus grown at 14 days of incubation
- Urine culture:  $<10,000$  colony-forming units/mL of *Enterobacter cloacae* complex isolated
- Cerebrospinal fluid: WBC count of  $314/\mu\text{L}$  ( $0.31 \times 10^9/\text{L}$ ) (67% neutrophils, 12% lymphocytes, 21% monocytes); red blood cell count of  $40 \times 10^6/\mu\text{L}$  ( $40 \times 10^{12}/\text{L}$ ), glucose of 44 mg/dL (2.4 mmol/L), protein of 27 mg/dL (.027 g/L)
- Cerebrospinal fluid Gram stain: Few WBCs; no organisms seen
- Cerebrospinal fluid culture: No growth of bacteria, yeast, or fungi

#### Radiographic Studies

- Echocardiography: Patent foramen ovale and patent ductus arteriosus with left-to-right shunts; normal left ventricle structure, size, and systolic function; no or valvular lesions seen
- Abdominal ultrasonography: No focal hepatic, splenic, or renal lesion seen
- Cranial ultrasonography: Bilateral grade 3 germinal matrix hemorrhages

The infant remained hemodynamically stable. She required increased supplemental oxygen but without increased ventilator needs. The lesions remained relatively stable in size, but both lesions developed necrotic centers. An ophthalmologic examination was negative for retinal lesions.

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a premature infant with nodular or necrotic skin lesions includes:



- Subcutaneous fat necrosis
- Septic emboli
- Ecthyma gangrenosum
- Cutaneous fungal infection
- Disseminated fungal infection

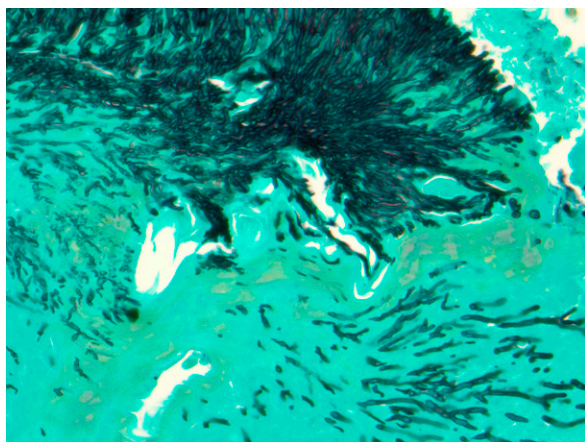
## ACTUAL DIAGNOSIS

### Cutaneous Fungal Infection

The neonatal team urgently consulted the pediatric infectious diseases and plastic surgery teams. The team started intravenous liposomal amphotericin B (3 mg/kg once daily). Punch biopsies of the lesions demonstrated focal dermal necrosis and abundant fungal hyphae (Fig 2). After fungal hyphae were observed on biopsy, the plastic surgery team performed excisional debridement of the right flank down to the muscle, with 1 cm of grossly normal margins.

Gross excisional biopsies demonstrated 3-mm margins free of hyphae. After 4 days of incubation, all fungal cultures from the tissue specimens that underwent biopsy and were excised grew *Aspergillus fumigatus* (Fig 3).

Antifungal susceptibility testing revealed a minimum inhibitory concentration of 5 µg/mL for voriconazole. Amphotericin was transitioned to enteral voriconazole with goal troughs of 1.5 to 5 µg/mL. Serial ophthalmology examination findings were negative for endophthalmitis. Serial ultrasonography did not show any development of infectious lesions in the liver, spleen, kidneys, or brain; the brain ultrasound scan did show naturally progressing intraventricular hemorrhages. The excisional biopsy sites healed well over the coming weeks. The infant tolerated enteral feedings and growth parameters improved normally over time. She eventually weaned from the ventilator to room air.



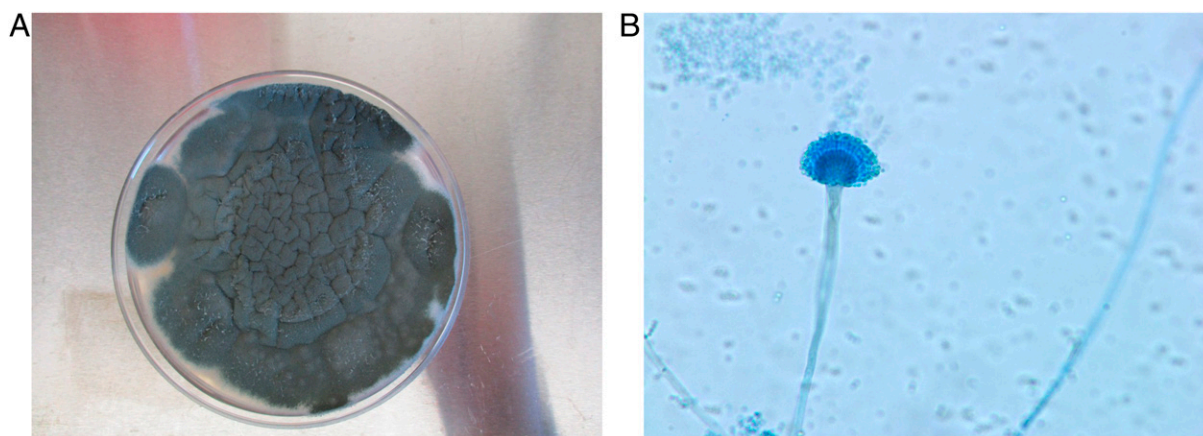
**Figure 2.** Silver stain at ×20 magnification demonstrating focal dermal necrosis and abundant fungal elements characterized by septated parallel-walled hyphae with acute angle branching.

Voriconazole was continued until the infant reached a postmenstrual age of 38 weeks' gestation and was then discontinued. The infant did not have any relapse in fungal disease. She was discharged from the hospital at 43 weeks' postmenstrual age.

## WHAT THE EXPERTS SAY

Cutaneous *Aspergillus* infections in extremely premature infants are rarely reported. Severe and invasive *Aspergillus* infections are most commonly seen in immunocompromised hosts, especially those with severe and prolonged neutropenia. (1) Primary cutaneous *Aspergillus* is a rare manifestation of aspergillosis in children and adults. Extremely premature infants are in a state of immune deficiency as a result of poor neutrophil chemotaxis and impaired cell-mediated immunity, which can predispose them to opportunistic fungal infections. (2) Extremely premature infants have been reported to develop both primary cutaneous *Aspergillus* as well as invasive and disseminated disease. (1)(2)(3)(4) Primary cutaneous disease is diagnosed after dissemination is excluded. (3) The diagnosis of cutaneous or disseminated fungal disease is often made by identifying the fungus on tissue specimens sent for biopsy, culture, and/or polymerase chain reaction–based tests. The sensitivity of fungal culture is highest when performed on tissue specimens, rather than swabbed collections. Cutaneous disease in extremely premature infants is often associated with breaks in their fragile skin, and in some cases, after the use of contaminated adhesives. (3) Construction in NICUs, allowing for increased *Aspergillus* conidia in the circulating air, has been associated with neonatal aspergillosis. (3) Because aspergillosis is rare in this population, prognosis and mortality are not well-established. Prompt recognition with antifungal treatment and surgical debulking of lesions may optimize outcomes, as was observed in this case.

In this infant, a diagnosis of subcutaneous fat necrosis was unlikely in the absence of predisposing risk factors (therapeutic hypothermia, neonatal asphyxia, maternal risk factors), and hypercalcemia. Moreover, the lesions were ulcerated, which is atypical for subcutaneous fat necrosis. The infant had negative blood cultures, and echocardiography did not show any valvular vegetation, making septic embolism unlikely. Ecthyma gangrenosum occurs almost exclusively in profound neutropenia, which this infant did not have. Given the high morbidity and mortality associated with disseminated fungal disease in extremely premature infants, this diagnosis was pursued aggressively. The appearance of necrotic skin lesions in extremely premature infants warrants prompt evaluation and treatment for cutaneous and



**Figure 3.** *Aspergillus fumigatus* morphologic features. A. Characteristic agar plate appearance of velvety blue-green growth with a narrow white perimeter. B. Characteristic microscopic uniseriate conidial heads.

disseminated fungal infections. Disease limited to the skin along with prompt surgical and medical management are likely important factors in improving survival.

## American Board of Pediatrics Neonatal-Perinatal Content Specification

- Cutaneous infections.

## References

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## ANSWER KEY FOR DECEMBER 2019 NEOREVIEWS

**Renal Replacement Therapy in Neonates:** 1. C; 2. B; 3. D; 4. A; 5. E

**Evaluation and Long-term Management of Neurogenic Bladder in Spinal Dysraphism:** 1. D; 2. E; 3. A; 4. C; 5. B

## A Neonate With Precordial Pulsations

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### QUESTION

Which of the following physical findings are demonstrated in the video (Video 1)?

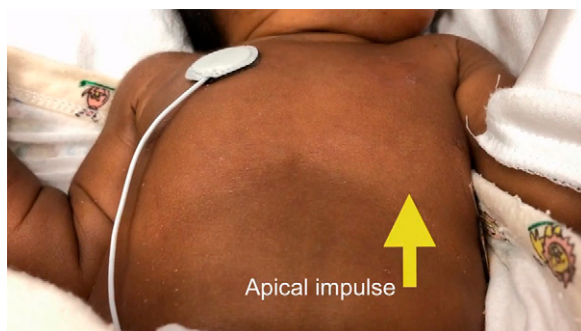
- a. Precordial bulge, suprasternal pulsations, and an apical impulse
- b. Precordial bulge, suprasternal pulsations, and a right parasternal heave
- c. Precordial bulge, suprasternal pulsations, a left parasternal heave, and epigastric pulsations
- d. Precordial bulge, suprasternal pulsations, a right parasternal heave, and an apical impulse
- e. Suprasternal pulsations, a left parasternal heave, epigastric pulsations, and an apical impulse



Video 1. What findings are seen on this video?

### FINDINGS

*Suprasternal pulsations* are pulsations that occur in the midline region above the suprasternal notch; in Video 2, these pulsations are observed below the infant's neck. They can be found in a neonate with hyperdynamic circulation or a dilated aortic arch. Both of these findings are seen in an infant with a patent ductus arteriosus with a large left-to-right shunt causing volume overload of the left ventricle. The left ventricle volume overload then increases the left



Video 2. Explanation of the findings seen in Video 1.

**AUTHOR DISCLOSURE** Drs Ou and Vachharajani have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



Figure 1. Chest radiograph showing cardiomegaly.

ventricular stroke volume in the aorta, resulting in a dilated aortic arch, which can be diagnosed on physical examination by identifying suprasternal pulsations. The increase in left ventricular stroke volume is explained by the Frank-Starling law, which states that within physiologic limits, the force of contraction of a muscle fiber is directly proportional to the initial length of the muscle fiber. Hyperdynamic circulation also may be seen in infants with anemia or thyrotoxicosis.

A left *parasternal heave* is a visible pulsation on the left side of the chest wall that may also be palpable. In Video 2, a left parasternal heave is appreciated when a finger placed on the chest is moved by the chest wall. In adults, the classic method of demonstrating this sign is observing a pencil rise and fall when placed perpendicular to the costal cartilages. It can also be demonstrated by placing a piece of paper on the area and watching it rise and fall. A parasternal heave can occur in an infant with right ventricular hypertrophy; when the hypertrophied right ventricle contracts, the left lower costal cartilages become more elevated. A left parasternal heave can also occur in a patient with an aneurysm of the descending aorta. A right parasternal heave does not exist.

*Epigastric pulsations* are pulsations that are seen below the xiphoid process in the midline on the anterior abdominal wall and can be visualized in Video 2. They are caused by a dilated right ventricle, hepatic pulsations, and an aneurysm of the descending aorta. A dilated right ventricle is diagnosed by feeling the pulsation on the tip of the finger in the epigastrium. A pulsating aortic aneurysm is felt on the pad of the palpating finger. A pulsating left lobe of the liver is associated with hepatomegaly.

An *apical impulse* or apex beat is also known as a point of maximum intensity (PMI) and is shown in Video 2. The

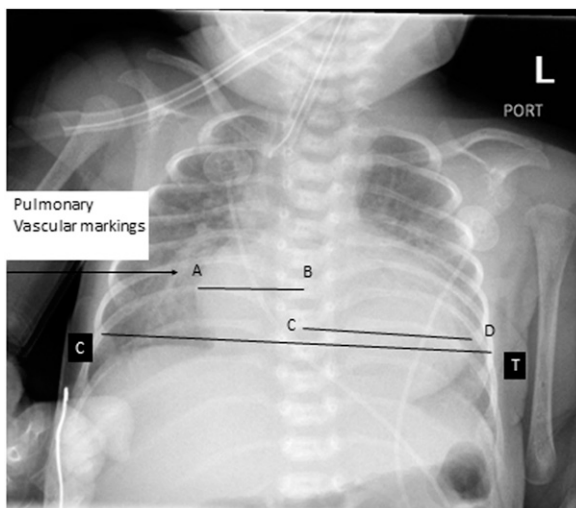


Figure 2. Chest radiograph with landmarks used to diagnose cardiomegaly.

term PMI is a misnomer because it also describes the site on the chest wall where a murmur is loudest. The PMI can be caused by maximum precordial pulsations because of a dilated pulmonary artery, a large right ventricle, ventricular aneurysm, or an aortic aneurysm. An apex beat refers to the apex of the left ventricle.

The neonate depicted in the videos has a double outlet right ventricle with a large patent ductus arteriosus that explains these physical findings. The accompanying chest radiograph (Fig 1) demonstrates an enlarged heart and increased pulmonary vascular markings. Cardiomegaly can be evaluated by adding lines AB and CD and dividing by line CT (Fig 2). The infant was referred for coiling of the patent ductus arteriosus to reduce the left-to-right shunting and relieve the heart failure.

The infant in the videos does not have a precordial bulge, which is a marker of longstanding cardiac enlargement. It would be seen as a prominence of the left chest wall area overlying the heart.

#### Correct Response

e. Suprasternal pulsations, a left parasternal heave, epigastric pulsations, and an apical impulse

### American Board of Pediatrics Neonatal-Perinatal Content Specification

- Recognize the clinical features of a neonate with a left-to-right shunt lesion.

## ACKNOWLEDGMENT

We wish to thank Bryan Camp from media services at St Louis Children's Hospital for editing the videos.

## Suggested Reading

Constant J. Inspection and palpation of the chest. In: *Essentials of Bedside Cardiology*. 2nd ed. Totowa, NJ: Humana Press; 2002; chap 5:89–111